REMARKS

Claims 35-42 and 44-58 were pending in the present application before entrance of the present Amendment. Claims 35-42 and 44-58 stand rejected. Claims 35, 46, and 58 are amended by the present Amendment. Applicant submits that no new matter has been added to the application by these amendments. Applicant respectfully requests reexamination and reconsideration of the claims, as amended. Each of the rejections levied by the Examiner is addressed in turn below.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 35-42 and 44-58 stand rejected by the Examiner under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner maintains that the specification, while being enabling for a pharmaceutical composition for "treating" cardiac arrhythmias, does not reasonably provide enablement for "preventing" cardiac arrhythmias.

Claims 35-42 and 44-58 are directed to pharmaceutical compositions for suppressing aberrant electrical activity in an electrically excitable tissue such as the brain, heart, and uterus that is effective to treat epilepsy, cardiac arrhythmias, or pre-term labor. According to the Examiner, the application fails to provide an enabling disclosure for the full scope of the claimed subject matter (Office Action on page 2). Applicant respectfully disagrees.

Applicant notes that the Examiner must consider not just a single factor, but a totality of the circumstances involving many factors when making a determination that the claims not enabled. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicant submits that an analysis of the *Wands* factors weighs in favor of Applicant's assertion of enablement of the full scope of the claims, as discussed in detail below.

Breadth of the Claims

The breadth of the claims is reasonable in view of the teachings in the specification, as described further below in view of the other *Wands* factors. Applicant disagrees with the assertion by the Examiner that the instant specification does not reasonably provide enablement for preventing cardiac arrhythmias. Drugs that prevent cardiac arrhythmias are known in the art and include beta blockers, potassium channel blockers, and other compounds such as those disclosed in

the instant Application on page 13, line 22 to page 14, line 7. Thus, one of ordinary skill in the art would be able to identify subjects at risk of cardiac arrhythmia and would be able to select a suitable antiarrhythmic agent for preventing cardiac arrhythmia without undue experimentation.

Nature of the Invention

The nature of the invention is a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue effective to treat epilepsy, cardiac arrhythmias, or pre-term labor. The composition comprises a site 1 sodium channel blocker, a local anesthetic, a glucocorticoid receptor, and an additional component selected from the group consisting of antiepileptic drugs, tocolytic agents, and antiarrhythmic agents.

State of the Prior Art

The state of the prior art is advanced. Applicant describes the state of the art in the specification and indicates that oral pharmacology has been used previously to decrease or eliminate unwanted activity leading to disorders in electrically excitable tissues (see, for example, page 1, lines 16-23, of the specification). Applicant takes issue with the assertion by the Examiner that "the skilled artisan would view that prevention of cardiac arrhythmias totally, absolutely, or permanently, so as to not even occur is highly unlikely." Those of ordinary skill in the art, for example, physicians, routinely prescribe medications for the prevention of cardiac arrhythmias. A cardiac arrhythmia is a potentially life-threatening condition for which it is desirable to prevent the occurrence of an arrhythmia. Medication may totally prevent arrhythmias in some subjects, whereas in other subjects medication may reduce the frequency of arrhythmias. It is understood in the art that a variety of factors including genetic, environmental, and dietary may affect the efficacy of a medication. Although total, absolute, or permanent elimination of arrhythmias is desirable, such a result is not necessary. Since no medication is 100% effective in the population, decreasing the chances of arrhythmias is sufficient. Regardless, independent claim 35 does not require that arrhythmias be prevented from ever occurring rendering the rejection of this claim, and the claims that depend therefrom, moot.

Level of Ordinary Skill in the Art

The level of ordinary skill in the art is high, requiring an M.D. and/or Ph.D. degree with postdoctoral training. The relevant arts include medicine, pharmaceutical science, polymer chemistry, medicinal chemistry, and the treatment of disease states involving deleterious electrical activity in excitable tissues. The skilled artisan is generally familiar with methods for preparing pharmaceutical compositions comprising anti-epileptic drugs, tocolytic agents, or antiarrhythmic agents and prescribing or administering such compositions.

Level of Predictability of the Art

The Examiner asserts that the skilled artisan would view treatment to prevent cardiac arrhythmias totally, absolutely, or permanently, as highly unpredictable. Applicant notes that amended independent claim 35 does not require that cardiac arrhythmias be prevented.

Applicant respectfully disagrees that, in view of the state of the art and Applicant's teaching, this factor weighs against enablement. Applicant notes that the specification discloses a number of compounds for the treatment of cardiac arrhythmias and that the general effectiveness of these compounds in connection with treating or preventing cardiac arrhythmias is known. See, for example, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th Edition, pages 841-873, submitted herewith. It is well known in the art that a physician may independently administer a plurality of drugs at a variety of doses to a subject to determine an effective treatment for that particular subject. Although the effectiveness of a specific drug indicated for the prevention of cardiac arrhythmias may not necessarily be known *a priori*, it is without undue experimentation and within the ability of one of ordinary skill in the art to select an effective drug, for example, based on the results of trial and error or correlation between the effectiveness of a drug and one or more characteristics of a particular subject to be treated. As noted in "State of the Prior Art" section above, prevention of cardiac arrhythmias is not limited to instances where arrhythmias are totally, absolutely, or permanently prevented but includes instances where the likelihood of a subject experiencing a cardiac arrhythmia is reduced. Thus, one of skill in the art using the inventive compositions to treat or prevent cardiac arrhythmias, would be able to determine, without undue

experimentation, whether and to what extent a given composition within the scope of the present claims would be effective in treating and preventing such conditions.

Amount of Direction Provided

The amount of direction provided by the Applicant in the specification is substantial. The specification (see, for example, page 19, line 20, to page 21, line 13) and the prior art provide various techniques that are applicable to methods for administration of such compositions. The specification at page 19, lines 18-19, discloses how to diagnose a patient with cardiac arrhythmias. Administration profiles and combination ratios of the active agents are readily determined by those of ordinary skill in the art based on the specification, further in view of data in the prior art. One of skill in the art could readily determine the effective level of each of these characteristics by routine experimentation based on this information.

Existence of Working Examples

The existence of working examples is not a necessary requirement to establish whether or not undue experimentation would be needed to practice the claimed invention. However, examples are provided on page 5, lines 4-17, and page 7, lines 5-8. These examples are believed to provide enough information for one of ordinary skill in the art to make and use the claimed invention.

Quantity of Experimentation Needed

The amount of experimentation required to practice the invention within the scope of the claims that stand rejected on this ground, in view of the totality of teachings of the specification of this application and the state of the art, is believed to be no more than routine experimentation. Applicant respectfully disagrees that those of ordinary skill in the art would view preventing cardiac arrhythmias as highly unpredictable. As noted above, because agents that prevent cardiac arrhythmias are disclosed in the specification and known in the art, Applicant believes one of ordinary skill in the art would be able to select an agent for treating or preventing cardiac arrhythmias for use in the compositions of independent claim 35 without undue experimentation. As noted above, one of skill in the art would recognize that the effectiveness of an agent will vary

among subjects in a population and that some subjects may respond better (*i.e.*, the agents prevent cardiac arrhythmias completely) than others (*i.e.*, the agents reduce the likelihood of cardiac arrhythmia). It is within the realm of routine experimentation for one of skill in the art, such as a clinician, to determine the most effective agent for a particular subject. Furthermore, in view of the fact that it is understood in the art that a cardiac arrhythmia is a deleterious condition, therapeutic benefit is achieved both by treating the arrhythmia to eliminate this condition and by practicing preventative medicine whereby the likelihood of a subject experiencing an arrhythmia is reduced. Applicant notes that prevention is not a binary term where cardiac arrhythmia is either prevented totally, absolutely, or permanently or not at all. Rather, prevention encompasses the range between these extremes, inclusive of total, absolute, or permanent prevention. It is a common and accepted occurrence that agents have variable efficacy within a population of subjects, thus it is not unlikely that prevention efficacy is also variable. A survey of the art (including references cited in the specification, references of record in the present application, and submitted herewith) provides evidence of the fact that such methods in general are known to those skilled in the art.

Therefore, a full and fair analysis of the *Wands* factors strongly suggests that the Applicant has enabled the claimed invention throughout its full scope. Accordingly, withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Applicant has amended the term "agent for treating or preventing cardiac arrhythmias" to the term "anti-arrhythmic agent" in the claims since this is a more commonly used name for such agents. Support for the use of this term can be found on page 5, line 6, of the originally filed specification. By making such a change in nomenclature, Applicant is not conceding the Examiner's position regarding treating and preventing and is not surrendering any claim scope.

Rejection under 35 U.S.C. § 103(a)

Claims 35-36, 39-42, 44-51 and 56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over published international PCT patent application, WO 98/51290 ("Kohane") in view of U.S. Patent Application Publication 2002/0010194 ("Levin") and U.S. Patent No. 6,133,299 ("Taylor"). The combination of Kohane, Levin, and Taylor do no render obvious the claimed invention. As noted by the Examiner, Kohane does not teach an additional component including

anti-epileptic drugs or that the electrically excitable tissue is brain tissue. To remedy this deficiency, the Examiner has combined Kohane with Levin and Taylor; however, there is no teaching or suggestion cited by the Examiner to combine these references. The three references merely provide the various components of the claimed composition in one form or another, but there is no teaching to combine particular components as recited in the pending claims to form the claimed compositions. There is certainly no teaching or suggestion in the combined references to prepare a composition comprising a site 1 sodium channel blocker, a local anesthetic, a glucocorticoid receptor agonist and an additional component selected from the group anti-epileptic drugs, tocolytic agents, and anti-arrhythmic agents, as in claim 35. Rather the Examiner seems to have impermissibly used the present Application as a blueprint to construct the claimed invention out of the prior art. The Examiner has not estabished a *prima facie* case of obviousness; therefore, Applicant requests that the rejection be removed.

Claims 35-36, 39-42, 44-51, and 57-58 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kohane in view of U.S. Patent Application Publication 2001/002404 ("Webb"), U.S. Patent No. 5,756,497 ("Bell"), U.S. Patent No. 5,387,419 ("Levy"), and Fauza *et al.* (*J. Pediatric Surgery*, 1999, 34, 540-542) ("Fauza"). The combination of Kohane, Webb, Bell, Levy, and Fauza also do not render obvious the claimed invention. The Examiner asserts that Kohane does not teach an additional component selected from the group consisting of tocolytic agents or anti-arrhythmic agents or that the electrically excitable tissue is heart or uterine tissue. To remedy this deficiency, the Examiner combined Kohane with Webb, Bell, Levy, and Fauza; however, there is no teaching or suggestion cited by the Examiner to combine these references. The five references merely provide the various components of the claimed composition in one form or another, but there is no teaching to combine particular components as recited in the pending claims to form the composition. There is certainly no teaching or suggestion in the combined references to prepare a composition comprising a site 1 sodium channel blocker, a local anesthetic, a glucocorticoid receptor agonist, and an additional component selected from the group consisting of anti-epileptic drugs, tocolytic agents, and anti-arrhythmic agents, as in claim 35. Rather the Examiner seems to have impermissibly used the present Application as a blueprint to construct the claimed invention

out of the prior art. The prior art does not render obvious the claimed invention; therefore, the Applicant requests that the rejection be removed.

Applicant wishes to note that the Examiner point out that claims that require no more than mixing together two or three conventional herbicides are *prima facie* obvious subject matter. Applicant requests clarification regarding this point as the instant claims do not recite herbicides.

Claims 52-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kohane in view of Levin, Taylor, and U.S. Patent No. 6,352,683 ("ten Cate"). Claims 52-54 depend from independent claim 35. For the reasons noted above, it is believed that independent claim 35 is patentable. Dependent claims 52-54 should therefore also be patentable. Accordingly, it is respectfully requested that the rejection of dependent claims 52-54 also be withdrawn.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825, under Docket No. M1237.70024US01, from which the undersigned is authorized to draw.

Dated: October 29, 2009

Respectfully submitted,

By /C. Hunter Baker/
C. Hunter Baker, M.D., Ph.D.
Registration No.: 46,533
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

CHAPTER

35 ANTIARRHYTHMIC DRUGS

J. Thomas Bigger, Jr., and Brian F. Hoffman

Drug therapy for cardiac arrhythmias is based on knowledge of the mechanism, consequences, and natural history of the arrhythmia to be treated and on a clear understanding of the pharmacology of the drugs to be used. The latter includes knowledge of drug action on the electrophysiological properties of normal and abnormal cardiac tissues, of their effects on the mechanical properties of the heart and vasculature, and of their interactions with the autonomic nervous system and their effects on other organ systems. Optimal therapy of cardiac arrhythmias requires an appreciation of the pharmacokinetic properties of antiarrhythmic drugs and how they are affected by disease. Finally, a broad knowledge of adverse effects of the agents and their potential interactions with other drugs is necessary to monitor the course of therapy.

CARDIAC ELECTROPHYSIOLOGY

Resting Potential. There is a voltage difference across the surface membrane of all cardiac cells, the resting transmembrane voltage or potential (*Vm*). For most cardiac cells, the resting *Vm* is about −80 to −90 mV relative to the extracellular fluid. The resting transmembrane concentration gradients for ions such as Na^+ and K^+ are established by active transport. Typical values for concentrations of ions in myocardial cells (*i*) and in extracellular fluid (*o*) (in millimoles per liter of water) are $[K]_o = 4.0$, $[K]_i = 150$, $[Na]_o = 140$, and $[Na]_i = 6$ to 12. If there were no voltage gradient across the membrane and the membrane were semipermeable to an ion, such as K^+, K^+ would diffuse out of the cell until the concentrations inside and outside were equal. However, the Na^+–K^+ exchange pump counteracts diffusional forces. In addition, fixed negative charges in the cell attract K^+ and counteract the concentration gradient that promotes diffusion. When these forces are equal, no net flux of ions will occur. The Nernst equation can be solved for the voltage that will maintain the existing transmembrane concentration gradient for a particular cation at a constant value—the equilibrium voltage E_X for a monovalent cation X:

$$E_X = \frac{RT}{F} \ln \frac{[X]_o}{[X]_i},$$

where $[X]_o$ is the concentration of the ion in extracellular fluid, $[X]_i$ is the intracellular concentration, R is the gas constant, T is the absolute temperature, and F is the Faraday constant. Given the ion concentrations listed above, $E_K = -97$ mV and $E_{Na} = +65$ mV. Since the resting membrane is permeable primarily to K^+, the resting *Vm* is close to E_K. However, other ions, such as Na^+, make small contributions to the resting *Vm*, as does the Na^+–K^+ pump (because it exchanges 3 Na^+ for 2 K^+).

Action Potentials. When cardiac cells are excited a complex sequence of voltage changes occurs as a function of time, due to changes in ionic conductances across the membrane. A typical transmembrane action potential of a Purkinje fiber is diagrammed in Figure 35–1, *A*. The action potential is divided into phases for purposes of description and discussion. Phase 0 = rapid depolarization; phase 1 = rapid repolarization to the plateau level of voltage; phase 2 = the plateau of the action potential; phase 3 = rapid repolarization; and phase 4 = the diastolic voltage time course. A variety of action potentials are seen in the normal heart. Action potentials of sinus and atrioventricular (AV) nodal cells have a slowly rising phase 0, and phases 1, 2, and 3 are not clearly distinguished from one another. Also, many cells have a steady value of *Vm* during phase 4, whereas others depolarize spontaneously during this period. Automatic fibers in the sinus node and His–Purkinje system reach a maximal negative value of *Vm* at the end of phase-3 repolarization, which is followed by spontaneous depolarization; excitation occurs when the *Vm* achieves the critical threshold voltage. The firing rate of a normally automatic cell is determined by (1) the value of maximal diastolic voltage, (2) the slope of phase-4 depolarization, and (3) the value of the threshold voltage. When a cell or group of cells undergoes self-excitation by this process and initiates an impulse that propagates to the rest of the heart, it is known as a *pacemaker*.

The ionic basis for the cardiac action potential continues to be the subject of active study. Although the voltage clamp technique has revealed clearly the ionic basis of action potentials in nerves, there are serious technical problems in the application of this technique to cardiac muscle. It has been most successfully used in cardiac Purkinje fibers. More recently, ionic currents have been investigated by the voltage clamp technique using

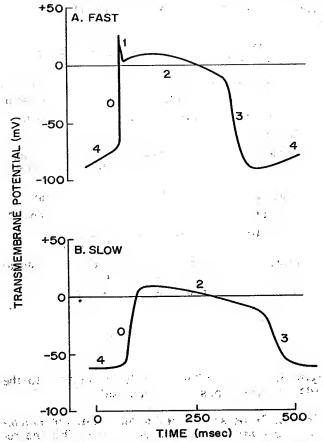


Figure 35–1. *Diagrammatic representation of fast and slow responses from mammalian cardiac Purkinje fibers.*

A. Fast Response. The phases of the normal fast response are shown: depolarization (*0*), repolarization (*1, 2, 3*), and the diastolic phase (*4*). Note the spontaneous phase-4 depolarization in this example. The rate of rise of phase 0 is rapid, and propagation will be rapid.

B. Slow Response. The slow response is initiated from a reduced (less negative) level of diastolic transmembrane voltage, shows slow depolarization, and has a long duration. Such an action potential propagates exceedingly slowly and leaves a long refractory wake.

single cardiac cells or isolated patches of plasma membrane (Grant and Starmer, 1987; Tseng *et al.*, 1987; Cohen *et al.*, 1989). Current concepts of the genesis of the cardiac action potential have been reviewed by Noble (1984), Baumgarten and Fozzard (1986), Brown and Yatani (1986), Cohen and colleagues (1986), and Pelzer and Trautwein (1987). A summary of the important ionic currents is given in Table 35–1.

Phase 0. In most cardiac cells, phase 0 is generated by the movement of Na^+ through selective channels that are activated in a voltage-dependent manner when the propagating cardiac impulse or spontaneous phase-4 depolarization causes the hypothetical *m* gate in the channel to open. The inward Na^+ current, i_{Na}, is very intense but very brief; it is terminated by a process called *inactivation*—rapid closure of a hypothetical gate (the *h* gate) in the Na^+ channel. After inactivation, the Na^+ channel does not open again until it has been reactivated by repolarization. Thus, the Na^+ channel can exist in one of three states: resting, active, or inactivated. Most of the Na^+ channels are closed during the plateau of the action potential, but a few are open, thereby permitting a small (inward) Na^+ current to flow.

Phase 1. Quick repolarization to the plateau of the action potential is brought about by several factors: the passive electrical properties of Purkinje fibers; inactivation of i_{Na}; and activation of i_{to1}, a transient outward (K^+) current (Tseng and Hoffman, 1989).

Phase 2. The plateau of the action potential is one of the most unusual features of the cardiac action potential. Membrane conductance is lower during the plateau than during diastole (phase 4). Although two Ca^{2+} channels, designated L and T, are activated on depolarization, the L channel (sensitive to Ca^{2+}-channel blockers) is primarily responsible for the current, i_{Ca}, that flows during the plateau (Bean, 1985). This current is inactivated in a manner analogous to the inactivation of i_{Na}, but the time constant for inactivation of i_{Ca} is much greater (50 msec as compared with 0.5 msec). Therefore, i_{Ca} declines slowly during the plateau. Because of low membrane conductance, small changes in any ionic current can have a marked effect on the time course of voltage during phase 2.

Phase 3. A time-dependent outward current that is carried primarily by K^+ (i_K) plays an important role in terminating the plateau and causing the fiber to repolarize to normal diastolic values of *Vm* (Gintant *et al.*, 1985). The i_K channel opens at about −40 mV, with a time constant of about 0.5 second. By the end of the plateau, i_K has waxed to a considerable value, while i_{Ca} has waned. Phase 3 is primarily the result of activated i_K in the presence of inactivating i_{Ca}. On repolarization, the i_K channel closes promptly and it remains closed at values of *Vm* more negative than −50 mV.

Phase 4. In many cells (*e.g.*, ordinary atrial or ventricular muscle), *Vm* is constant during diastole; these cells will rest indefinitely until activated by a propagating impulse or an external stimulus. However, as mentioned above, other cells exhibit spontaneous phase-4 depolarization and self-excitation (*i.e.*, automaticity; *see* Figure 35–1, *A*). This type of behavior is characteristic of the sinus node, AV node, and the His–Purkinje system. The main determinant of phase-4 depolarization is the pacemaker current (i_f) (DiFrancesco, 1981a, 1985). The i_f begins to activate when the *Vm* becomes more negative than −50 mV and progressively activates during diastole to depolarize the fiber. Both Na^+ and K^+ contribute to i_f (DiFrancesco, 1981b). Several other ionic currents modulate phase-4 depolarization. Electrogenic extrusion of Na^+ can be an important part of background outward current. Also, Ca^{2+} current flowing through T channels may be important during the latter part of phase 4 (Hagiwara *et al.*, 1988). Spontaneous activity of

Table 35–1. IONIC CURRENTS AND THE PURKINJE FIBER ACTION POTENTIAL

CURRENT	MAJOR ION RESPONSIBLE FOR THE CURRENT	PHASE OF ACTION POTENTIAL	REVERSAL VOLTAGE (mV)	DIRECTION OF CURRENT FLOW	PHYSIOLOGICAL ROLE
i_{Na}	Na^+	0	+65	Inward	Depolarizes fiber during phase 0
i_{to1}	K^+	1	−50 to −80	Outward	Rapid repolarization in phase 1
i_{to2}	K^+	1	?	Outward	Role uncertain
$i_{Ca,L}$ *	Ca^{2+}	1, 2	+60 to +80	Inward	Contributes to plateau of action potential; triggers the release of internal Ca^{2+}
$i_{Ca,T}$	Ca^{2+}	1, 2	+40	Inward	Physiological role uncertain
i_K	K^+	3	−70	Outward	Repolarizes fiber during phase 3
i_{K_1}	K^+	0, 1, 2, 3, 4	−90	Outward	Maintains resting potential, tends to repolarize fiber
i_f	Na^+	4	−10 to −20	Inward	Activation promotes spontaneous depolarization
i_{bi}	Na^+, Ca^{2+}	0, 1, 2, 3, 4	+40 †	Inward	Tends to depolarize fiber

* Referred to as i_{Ca} in text.
† Current is inward at voltages negative to E_K.

sinus nodal cells is faster than that of Purkinje fibers because i_f activates at a faster rate.

Fast and Slow Responses. Two categories of cardiac action potentials can be distinguished: *fast* and *slow* responses. Depolarization in the fast response (*see* Figure 35–1, *A*) is generated by an intense inward i_{Na}, has a large, fast-rising phase 0, propagates very rapidly, and has a large safety factor for conduction. Normal atrial, ventricular, and Purkinje fiber action potentials are examples of the fast response. The slow response has a slowly rising phase 0, propagates very slowly, and has a low safety factor for conduction (Figure 35–1, *B*). Action potentials of cells in the sinus and AV nodes are examples of slow responses seen under normal conditions. The main depolarizing current for slow responses is carried by Ca^{2+} and has the characteristics of the current that flows through L channels.

Excitability and Refractoriness. Excitability is traditionally measured in terms of the strength of an electrical pulse required to excite the heart. The functional significance of changes in excitability is difficult to determine. Therefore, little emphasis is placed here on the effects of antiarrhythmic drugs on excitability. Refractoriness has been defined in many different ways; in this discussion, refractoriness is used to refer to the duration of the effective refractory period (ERP), which is the minimal interval between two propagating responses. In cardiac cells with fast responses, the ERP is closely linked to action potential duration (APD), because recovery of Na^+ channels from inactivation closely parallels repolarization. In cardiac cells with slow responses, refractoriness can outlast full repolarization (*i.e.*, ERP is longer than APD) because i_{Ca} recovers only slowly from inactivation. Antiarrhythmic drugs prolong the ERP relative to the APD in many types of cardiac cells.

Responsiveness and Conduction. The term *membrane responsiveness* is used to describe the response of a cardiac fiber to a stimulus (*e.g.*, a propagating action potential or applied electrical pulse). Cardiac fibers do not regain their ability to develop a normal response until repolarization is complete. Changes in the maximal rate of depolarization during phase 0 (V_{max}) provide an index of changes in availability of the Na^+ conductance system or the degree of recovery from inactivation of the Na^+ channel. Phase-0 V_{max} is an important determinant of conduction velocity and block of premature impulses. In cardiac Purkinje fibers, the V_{max} of a response is very strongly dependent on Vm at the instant of excitation (*see* Figure 35–2). In normal fibers, the time constant for recovery from inactivation of the Na^+ channel is quite short, such that recovery of V_{max} is primarily a function of transmembrane voltage as repolarization occurs. Consequently, V_{max} is similar when a cardiac fiber is stimulated at a given level of Vm, regardless of whether the fiber is stimulated during phase-3 repolarization or during phase-4 depolarization. The time constant for recovery of Na^+ channels is significantly longer: (1) at low (more positive) values of Vm; (2) during treatment with antiarrhythmic drugs; and (3) in membranes altered by disease. The S-shaped relationship between V_{max} and Vm is typical not only of cardiac Purkinje fibers but also of atrial and ventricular muscle. Cells of the sinus node and the AV node do not regain full responsiveness until well after repolarization is complete. There is a considerable safety factor in cardiac muscle (except in the sinus and AV nodes), since V_{max} must be reduced to half or less of normal before conduction velocity decreases.

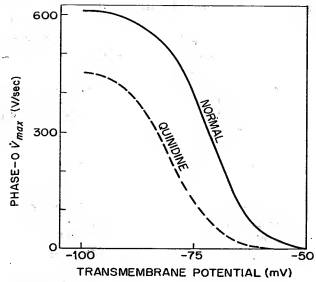


Figure 35–2. *Membrane responsiveness.*

Membrane responsiveness in a cardiac Purkinje fiber is depicted. The maximal rate of rise of depolarization during phase 0 is plotted as a function of transmembrane voltage at the time of activation. The solid line shows the relationship under normal conditions, and the dashed line depicts the effect of a moderate-to-high concentration of quinidine. Quinidine shifts the relationship on its voltage axis so that a reduced response is obtained at any given level of transmembrane voltage. Also, the maximal rate of depolarization is reduced.

MECHANISMS RESPONSIBLE FOR CARDIAC ARRHYTHMIAS

An arrhythmia is an abnormality of rate, regularity, or site of origin of the cardiac impulse or a disturbance in conduction that causes an alteration in the normal sequence of activation of the atria and ventricles. Clinically, ventricular arrhythmias are classified as benign, potentially malignant, or malignant based on the risk of their causing sudden death (*see* Table 35–2). Such arrhythmias may arise because of alterations in impulse generation, impulse conduction, or both.

Arrhythmias Due to Abnormalities of Impulse Generation

There are many examples of arrhythmias that arise because of either enhancement or failure of normal automaticity. Mechanisms of abnormal automaticity are also subjects of ongoing experimental interest.

Altered Normal Automaticity. When considering arrhythmias due to abnormalities of automaticity, it is important to recall that only a few types of cardiac cells frequently develop normal automaticity: sinus node, distal AV node, and the His–Purkinje system. Other cell types can develop automaticity as well, for example, specialized atrial fibers in the internodal tracts and fibers near the ostium of the coronary sinus.

Sinus Node. In the sinus node, rate can be altered by autonomic activity or intrinsic disease. Increased vagal activity can slow or stop sinus nodal pacemakers by increasing K^+ conductance (g_K); this increases outward K^+ currents, hyperpolarizes the pacemaker cells, and slows or stops their depolarization. Increased sympathetic traffic to the sinus node increases the rate of phase-4 depolarization, probably by a combination of effects (*e.g.*, increased rate of activation of the pacemaker current i_f; increased magnitude of i_{Ca}). Intrinsic disease of sinus nodal pacemaker cells seems to be responsible for faulty pacemaker activity in the sick sinus syndrome in man (Bigger and Reiffel, 1979; Kerr *et al.*, 1983). The precise mechanism and pathogenesis are still unknown.

Purkinje Fibers. Augmented automaticity in the His–Purkinje system is a common cause of arrhythmias in human subjects. Increased sympathetic nerve activity can cause a substantial increase in the rate of spontaneous firing. This increase is brought about by an ionic mechanism that is similar to the changes causing sinus tachycardia (DiFrancesco, 1981a). It is possible for AV junctional pacemakers to usurp control of the ventricles in the presence of a normal sinus node and normal AV conduction because of selectivity of traffic in sympathetic nerves (Randall, 1977). As a result, higher neural activity, including that associated with cardiovascular reflexes, can alter cardiac rate and produce disturbances of rhythm primarily by changing the pattern of firing of various subunits of the cardiac autonomic nerves (Levitt *et al.*, 1976). The effect of the vagus on the His–Purkinje system in man is not well understood. The response of Purkinje fibers to acetylcholine varies with species; acetylcholine slows normal pacemaker activity in the dog but accelerates it in sheep. In addition, many questions about functional vagal innervation of the His–Purkinje system are unsettled; it appears that vagal innervation of the proximal system may be significant, whereas that of the peripheral system is more sparse (Levy, 1977).

In disease, automaticity in the His–Purkinje system may become reduced. In the sick sinus syndrome it is typical for the ventricular pacemakers to be depressed as well as the sinus node (*see* Bigger and Reiffel, 1979). Thus, very long pauses in cardiac rhythm may occur when the sinus node fails as a pacemaker. In AV block due to widespread bundle-branch disease, the rate of ventricular pacemakers may also be abnormally slow. In neither of these examples has a mechanism been identified.

Abnormal Generation of Impulses. In addition to the arrhythmias caused by alterations of normal automaticity, numerous abnormal mechanisms for the generation of impulses have been observed in experimental preparations (*see* Cranefield and Aronson, 1988). Many of these mechanisms appear to fit into one of two categories—abnormal automaticity or triggered activity. Abnormal automatic-

Table 35–2. PROGNOSTIC CLASSIFICATION OF VENTRICULAR ARRHYTHMIAS *

	BENIGN	POTENTIALLY MALIGNANT	MALIGNANT
Risk for sudden death	Very Low	Low to moderate	High
Clinical presentation	Palpitations; detected by routine exam	Palpitations; detected by routine exam or screening	Palpitations; syncope; cardiac arrest
Heart disease	Usually absent	Present	Present
Cardiac scarring and/or hypertrophy	Absent	Present	Present
Left ventricular ejection fraction	Normal	Low to very low	Low to very low
Frequency of VPDs †	Low to moderate	Moderate to high	Moderate to high
Sustained ventricular tachycardia	Absent	Absent	Present
Hemodynamic effects of arrhythmia	Absent	Absent to mild	Moderate to severe

* The characteristics listed are typical, but there are exceptions (*e.g.*, benign ventricular arrhythmias can be frequent, and occasionally, repetitive).
† VPD = ventricular premature depolarization(s).

ity refers to spontaneous diastolic depolarization that occurs at a very low (relatively positive) value of *Vm* in a cell that normally has a much higher value of *Vm* in diastole. Triggered activity is the generation of impulses by afterdepolarizations that reach threshold (*see* below). Both of these mechanisms differ strikingly from those responsible for normal automaticity. Moreover, both of these mechanisms can cause the formation of impulses in fibers that ordinarily are incapable of automatic function (*e.g.*, ordinary atrial or ventricular muscle cells).

Abnormal Automaticity. Purkinje fibers, atrial cells, and ventricular cells can all show spontaneous diastolic depolarization and repetitive automatic firing when their resting *Vm* is reduced substantially (*e.g.*, to −60 mV or less negative values). The ionic mechanisms for such abnormal automaticity are not known, but i_K and i_{Ca} probably contribute to this behavior.

Early Afterdepolarizations. Early afterdepolarizations are secondary depolarizations that occur before repolarization is complete. Characteristically, the secondary depolarization commences at membrane potentials close to those present during the plateau of the action potential (*see* Figure 35–3, *A*). In isolated tissues, a burst of depolarizations often occurs, and is followed by a few damped oscillations, until, finally, *Vm* either rests at the range of the plateau voltage (about −20 to −40 mV) or returns to a relatively high resting value. Experimentally, early afterdepolarizations have been produced in cardiac Purkinje fibers by a number of maneuvers, including stretching, hypoxia, and chemical alterations. Early afterdepolarizations are promoted by (and may result from) (1) decreased background outward current (i_{K_1}), (2) increased background inward current (i_{b}), (3) increased residual i_{Na} during the plateau, (4) increased magnitude and/or duration of i_{Ca}, and (5) reduced magnitude of i_K. When the *Vm* of cardiac muscle fibers is in the range of the plateau voltage, the membrane conductance is low and tiny inward currents cause substantial depolarization.

Delayed Afterdepolarizations. A delayed afterdepolarization is a secondary depolarization that occurs early in diastole, that is, after full repolarization has been achieved (*see* Figure 35–3, *B*). The delayed afterdepolarization is not self-initiated but is dependent on a prior action potential. Delayed afterdepolarizations may be seen when certain cell types are exposed to catecholamines, digitalis, low $[K]_o$, or perfusates containing low $[Na]_o$ and high $[Ca]_o$. Delayed afterdepolarizations can reach threshold and give rise to a single premature depolarization. If the premature depolarization is followed by another delayed afterdepolarization, a second impulse may result. In this way, delayed afterdepolarizations can cause either coupled extrasystoles or runs of tachyarrhythmias. Several factors increase the amplitude of delayed afterdepolarizations and promote triggered activity. They include increased heart rate, premature systoles, increased $[Ca]_o$, catecholamines, and other drugs, particularly digitalis. The mechanism for delayed afterdepolarizations that arise in digitalis toxicity is discussed in Chapter 34. Delayed afterdepolarizations can readily be induced by digitalis in the His–Purkinje system and, with more difficulty, in specialized atrial or ordinary ventricular cells. The delayed afterdepolarizations induced by digitalis in Purkinje fibers are associated with an

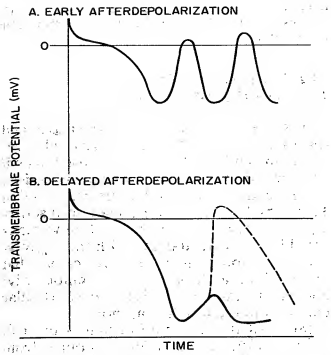


Figure 35–3. *Two forms of triggered activity in a cardiac Purkinje fiber.*

A. Early Afterdepolarization. Repolarization is interrupted by secondary depolarizations. Such responses may excite neighboring fibers and be propagated.

B. Delayed Afterdepolarization. After full repolarization is achieved, *Vm* again transiently depolarizes. If the delayed afterdepolarization reaches threshold, a propagating response can occur (dashed line).

abnormal transient inward current that is carried mainly by Na^+. It is reasonable to speculate that some clinical arrhythmias caused by digitalis (*e.g.*, coupled ventricular premature depolarizations and atrial or ventricular tachycardias) result from delayed afterdepolarizations. Also, some supraventricular tachycardias that arise in the absence of drug therapy may be triggered activity because of delayed afterdepolarizations.

Triggered Activity. As mentioned, when a delayed afterdepolarization reaches threshold, a single extrasystole may result or sustained repetitive firing may be triggered (Cranefield and Aronson, 1988). Activation by this mechanism must be initiated by an action potential; thus, it cannot arise *de novo*, as can a normal automatic rhythm. Although triggered activity cannot be self-initiated, it can be self-sustained. Triggered activity in cells that have delayed afterdepolarizations shares many characteristics with reentrant tachyarrhythmias (*see* below). As a result, it is difficult to know which mechanism is responsible for a given clinical tachyarrhythmia.

ARRHYTHMIAS CAUSED BY ABNORMALITIES OF IMPULSE CONDUCTION

Arrhythmias may arise by recirculating activation that is incited by an initiating depolarization. Such arrhythmias (often referred to as *reentrant arrhythmias*), like triggered rhythms, are self-sustained but not self-initiated. For reentry to be initiated, one-way block of conduction must occur, and there must be an anatomical or functional "barrier" to conduction that forms a circuit (*see* Bigger, 1973). Furthermore, the pathlength of the circuit must be greater than the wavelength of the cardiac impulse, where wavelength is the product of conduction velocity and the refractory period (*see* Figure 35–4). For reentry to occur, normal conduction must be greatly slowed, refractoriness markedly shortened, or both. Conduction is normally very slow in the sinus and AV nodes. Further slowing by premature activation or by disease easily creates conditions that permit reentry. Disease processes may also create conditions that permit reentry even in fibers that usually conduct the cardiac impulse at very rapid rates, such as cardiac Purkinje fibers. Usually, marked slowing of conduction is the abnormality that permits reentry. However, marked abbreviation of action potentials and of refractoriness can have a role as well. Con-

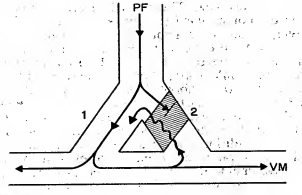


Figure 35–4. *Reentry.*

The diagram shows one of the forms of reentrant reexcitation in the ventricle (Schmitt and Erlanger, 1928–29). A branched Purkinje fiber (*PF*) terminates on a strip of ventricular muscle (*VM*). The shaded area in branch 2 represents a depolarized area that is the site of a one-way block; thus, orthograde sinus impulses are blocked in this area, but retrograde responses are propagated successfully. Retrograde conduction in branch 2 is slow enough for cells in branch 1 to recover and respond to the reentering impulse. A single reactivation of branch 1 will produce a single ventricular premature depolarization; continuous conduction around the circuit will cause ventricular tachycardia.

Antiarrhythmic drugs can abolish such reentrant activity by producing two-way block in branch 2 or by improving conduction in branch 2, that is, by removing the one-way block.

duction may be slowed because of alterations in the fast response or development of slow responses.

Altered Fast Response. When resting Vm is more depolarized than −75 mV (as with stretch or high $[K]_o$), $\dot{V}_{max}$ and conduction velocity decrease substantially because of voltage-dependent inactivation of the fast Na^+ channel (*see* Figure 35–2). When resting Vm is between −50 and −65 mV, conduction velocity is greatly reduced and abnormal "fast responses" can propagate slowly enough to permit reentry. If Vm is more positive than −50 mV or so, Na^+ channels will be almost totally inactivated and fast responses cannot be elicited. At such low values of Vm, fast responses may conduct decrementally; that is, the adequacy of the propagating response as a stimulus to resting tissue in its path lessens progressively as it propagates in depolarized tissues. Under such conditions, a delicate balance exists that determines whether conduction succeeds or fails.

Slow Responses and Very Slow Conduction. Slow action potentials appear in cardiac Purkinje fibers when they are exposed to increased $[K]_o$ and catecholamines. In the voltage range at which slow potentials emerge, i_{Na} is inactivated and the pacemaker current i_f is fully deactivated; thus, these currents are unlikely to have a role in the genesis of the slow response. The inward current that causes the slow potential is i_{Ca}. Because this current is relatively small in magnitude, slow responses are more likely to develop when background outward currents are decreased. Typically, slow responses are 40 to 80 mV in amplitude, depolarize at 1 to 2 V per second (*i.e.*, about 0.002 the rate of the fast response), and last for 0.4 to 1 second (*see* Figure 35–1, *B*). As a result, slow responses propagate so slowly that reentry can occur in very short pathways. In addition, the duration of the action potential and refractoriness may shorten dramatically just proximal to the site of block because of a repolarizing current provided by neighboring resting tissue. The short duration of the refractory period in tissue at the site of unidirectional block permits reentry of subsequent impulses even if the reentry pathway is short.

Significance of Reentry. Reentry may occur in many sites in the heart; it is relatively easy to elicit in the vicinity of the sinus or AV nodes by the use of premature stimulation to slow conduction and to produce a functional one-way block, even in normal hearts. Clinically, reentry is the usual cause of paroxysmal supraventricular tachycardia. Reentry in the His–Purkinje system is thought to be one cause of coupled ventricular premature depolarizations and ventricular tachycardia in man. This idea is supported by extensive study in both man and animals. For example, Durrer and coworkers (1971) and El-Sherif and associates (1977) have shown, in experiments with acute myocardial infarction in dogs, that the cardiac impulse can meander through the infarcted region and emerge much later to produce ventricular premature depolarizations, ventricular tachycardia, or ventricular fibrillation.

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs have been grouped together according to the pattern of electrophysiological effects that they produce and/or their presumed mechanisms of action. Classifications such as the one presented in Table 35–3 are commonly used in discussing antiarrhythmic drugs, and physicians should thus be acquainted with them. However, it should also be recognized that drugs within a class do differ significantly: one may be effective and safe in a particular patient while another may not.

Much of the information that is used to classify antiarrhythmic drugs comes from experimental studies in animals (Arnsdorf and Wasserstrom, 1986). For example, the classification in Table 35–3 relies heavily on observations made with preparations of rabbit atria and canine or bovine cardiac Purkinje fibers. The agents in class I directly alter membrane conductances of cations, particularly those of Na^+ and K^+. It is useful to subcategorize these drugs in terms of their relative ability to depress $\dot{V}_{max}$ (by blockade of fast Na^+ channels) and to slow membrane repolarization. Class II includes agents that have primarily indirect effects on electrophysiological parameters by virtue of their ability to block β-adrenergic receptors. The agents in class III are mechanistically the least well defined. They share the capacity to delay membrane repolarization (and thus prolong refractoriness) with relatively little effect on $\dot{V}_{max}$. Finally, class-IV agents have relatively selective depressant actions on Ca^{2+} channels, primarily those of the L type.

Such schemes can lead to ambiguities. Some drugs have multiple actions and therefore belong in more than one class. It may not be clear in a particular case which of the drug's actions is responsible for its efficacy. Moreover, when drugs are given to patients with heart disease and arrhythmias, their effects on the central and autonomic nervous systems, on hemodynamics, or on myocardial ischemia or metabolism may greatly influence their antiarrhythmic action.

Table 35–3. CLASSIFICATION OF ANTIARRHYTHMIC DRUGS ACCORDING TO THEIR MECHANISM OF ACTION

CLASS	ACTION	DRUGS
I.	*Sodium Channel Blockade*	
A.	Moderate phase-0 depression and slow conduction (2+) *; usually prolong repolarization	Quinidine, procainamide, disopyramide, moricizine
B.	Minimal phase-0 depression and slow conduction (0 to 1+); usually shorten repolarization	Lidocaine, mexiletine, phenytoin, tocainide
C.	Marked phase-0 depression and slow conduction (3+ to 4+); little effect on repolarization	Encainide, flecainide, propafenone, indecainide
II.	*β-Adrenergic Blockade*	Propranolol, acebutolol, esmolol, others
III.	*Prolong Repolarization*	Amiodarone, bretylium, sotalol
IV.	*Ca^{2+}-Channel Blockade*	Verapamil, diltiazem

* Relative magnitude of effect on conduction velocity indicated on a scale of 1+ to 4+.

Use-Dependent Blockade of Ion Channels

An understanding of the effects of many antiarrhythmic drugs on the heart depends in part on knowledge of how those drugs interact with the gated channels that permit ionic currents across the sarcolemma (*see* Hondeghem and Katzung, 1977; Hille, 1978). This question has been evaluated in studies on single channels with the patch clamp technique (Ogden *et al.*, 1981) and on populations of channels by voltage clamping (Hondeghem and Katzung, 1980; Bean *et al.*, 1983; Gintant and Hoffman, 1983). The effects of local anesthetic antiarrhythmic agents on i_{Na} have been explained by assuming that the drugs bind to the Na^+ channel and block its function, with the result that Na^+ conductance remains at zero for as long as the drug is bound (*see* Hondeghem and Katzung, 1977; Hondeghem, 1987). The interaction of drug and channel can be represented as shown in Figure 35–5. *R*, *O*, and *I* represent the resting, open, and inactivated states of the channel, respectively; *D* is drug; and *R**, *O**, and *I** are the nonconducting forms of the channel to which drug is bound. *A* indicates the voltage- and time-dependent reactivation of the channel, and *A** is any modification of this process caused by drug. The diagram is greatly simplified and, in particular, ignores the fact that there are probably a number of transition states for the channel, as between *R* and *O*.

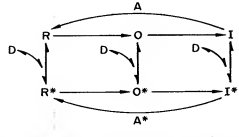


Figure 35–5. *Modulated-receptor hypothesis for the action of antiarrhythmic drugs.* (*See* text for explanation.)

In terms of this diagram, a drug such as lidocaine could interact with any or all of the three states of the channel. However, the drug may preferentially combine with channels in the *R*, *O*, or *I* state. This preference may reflect state-dependent affinities of the channel for the drug (modulated receptor hypothesis) or may result from state-dependent access to and/or egress from the vicinity of the binding site (guarded receptor hypothesis) (Starmer and Grant, 1985). In addition, the drug-channel complex need not undergo voltage-dependent transitions in the usual way. A more negative transmembrane potential might be needed for the $I^* \rightarrow R^*$ transition than for $I \rightarrow R$ or, alternatively, the drug might have to dissociate from channels in the I^* state for the $I \rightarrow R$ transition to occur.

For many local anesthetic antiarrhythmic drugs, it appears as if channel blockade is most likely when the channel is in the *O* or *I* state and that reactivation is slowed or incomplete at usual transmembrane voltages. The consequences of this are important for the actions of antiarrhythmic drugs. A concentration of drug that exerted a minimal effect on a quiescent fiber at normal resting potential could block a significant fraction of channels during one action potential. Also, to the extent that the $I^* \rightarrow R^*$ (or $I^* \rightarrow R$) transition is slowed, channels would accumulate in the I^* state during repeated action potentials and i_{Na} for each action potential would decrease until a steady state had been attained. This is the phenomenon of use-dependent block, and it has been described for all local-anesthetic antiarrhythmic drugs and for some Ca^{2+}-channel blocking drugs (*see* below; *see also* Chapter 32). In addition, some antiarrhythmic drugs appear to cause "tonic" (*i.e.*, not use-dependent) block of i_{Na} through interaction with channels in the *R* state.

If the association of drug with channel and dissociation of drug from channel are both relatively

rapid, use-dependent block will reach a steady state during the course of a few action potentials, and, if the interval between action potentials is reasonably long, little blockade will persist at the time of the upstroke of the action potential. If dissociation is quite slow, use-dependent block may not develop fully until there have been many action potentials, and a significant degree of block will be present at the time that each action potential is initiated. Finally, since a decrease in transmembrane voltage causes inactivation of fast channels, the effects of drugs on i_{Na} are enhanced in depolarized cells.

INDIVIDUAL ANTIARRHYTHMIC AGENTS

Discussion of the individual drugs is organized by class (*see* Table 35–3). The effects of each class of agent on the electrophysiological properties of specialized cardiac fibers are summarized in Table 35–4, while drug-induced alterations in the electrocardiogram (ECG) are listed in Table 35–5. The clinical usefulness of each agent is described in the text, and an overall estimate of their value in the management of specific arrhythmias is presented in Table 35–6. Pharmacokinetic parameters for the major agents are summarized in Appendix II.

CLASS I_A: QUINIDINE, PROCAINAMIDE, AND DISOPYRAMIDE

As noted above, class I_A antiarrhythmic drugs inhibit i_{Na}, depress phase-0 depolarization, and slow conduction velocity in myocardial Purkinje fibers to a moderate degree at normal resting values of *Vm* (*see* Table 35–3). These effects are intensified when the membrane is depolarized or when the frequency of excitation is increased. Although quinidine is often considered to be prototypical, procainamide does not have the capacity of quinidine and disopyramide to block muscarinic cholinergic receptors or the apparent ability of disopyramide to block Ca^{2+} channels. Some discussion of moricizine, an investigational agent, is included here even though it displays some of the characteristics of class I_B agents.

History. It was noted many years ago that patients with malaria who also had atrial fibrillation would occasionally be cured of the arrhythmia

Table 35–4. EFFECTS OF THERAPEUTIC CONCENTRATIONS OF ANTIARRHYTHMIC DRUGS ON ELECTROPHYSIOLOGICAL PROPERTIES OF SPECIALIZED CARDIAC FIBERS *

	CLASS OF ANTIARRHYTHMIC DRUG					
	I_A	*I_B*	*I_C*	*II*	*III*	*IV*
Sinus node						
Automaticity	0, ↑	0	0	↓	↓, ↑ †	↓
AV node						
Effective refractory period (ERP) ‡	↓, 0, ↑	0, ↓	↑	↑	↓, 0, ↑	↑
Purkinje fibers						
Action potential amplitude	↓	0, ↓, ↑	↓	0	0	0
Phase-0 $\dot{V}_{max}$	↓	0, ↓, ↑	↓	0, ↓	0, ↓	0
Action potential duration (APD)	↑, ↓	↓	↓	↓, 0, ↑	↑	0, ↓
Effective refractory period (ERP)	↑, ↓	↓	↓	↓, 0, ↑	↑	0, ↓
ERP/APD	↑	↑	↑	↑	0	0
Membrane responsiveness	↓	0, ↓	↓	↓	0	0
Automaticity	↓, 0	↓	↓	↓	↓, ↑ †	0, ↓

* Changes are indicated as follows: ↓, decreased; 0, no change; ↑, increased; where bidirectional arrows are shown, there is variability in the direction of change. Boldface arrows indicate effects of greater magnitude.
† Bretylium only; due to release of catecholamines on initial exposure to the drug.
‡ Due to a complex balance of direct and indirect autonomic effects.

Table 35–5. EFFECTS OF THERAPEUTIC CONCENTRATIONS OF ANTIARRHYTHMIC DRUGS ON SINUS RATE AND ELECTROPHYSIOLOGICAL AND ELECTROCARDIOGRAPHIC INTERVALS *

	CLASS OF ANTIARRHYTHMIC DRUG					
	I_A	I_B	I_C	*II*	*III*	*IV*
Sinus rate	0, ↑	0	0	↓	↓	↓
P–R	0, ↑	0	↑	↑	↑	↑
A–H	↓, 0, ↑	0, ↓	↑	↑	↑	↑
H–V	0, ↑	0	↑	0	0, ↑	0
QRS	↑	0	↑	0	0	0
Q–T_c †	↓, 0, ↑	↓	↑	↓, 0, ↑ ‡	↑	0
JT §	↓, 0, ↑	↓	↓	↓, 0, ↑ ‡	↑	0
Ventricular rate in atrial fibrillation	0, ↑	↓, 0, ↑	↓, 0, ↑	↓	↓	↓

* Changes are indicated as follows: ↓, decreased; 0, no change; ↑, increased; where bidirectional arrows are shown, there is variability in the direction of change. Boldface arrows indicate effects of greater magnitude.
† The Q–T_c interval is the Q–T interval corrected for heart rate.
‡ Depends on the drug (*e.g.*, propranolol shortens, sotalol lengthens).
§ J–T interval = Q–T_c – QRS.

when they were treated with cinchona. Perhaps the earliest recorded reference to the use of cinchona in atrial fibrillation is that by Jean-Baptiste de Sénac of Paris in 1749 (*see* Willius and Keys, 1942). Years later Wenckebach (1914) reported on the effect of quinine alkaloids in certain cardiac arrhythmias. Impressed by this report, Frey (1918) studied the use of cinchonine, quinine, and quinidine (an optical isomer of quinine) in patients with atrial fibrillation and found quinidine to be the most effective.

In 1936, Mautz demonstrated that application of procaine elevated the threshold of ventricular muscle to electrical stimulation. Extension of this observation by numerous workers established that the cardiac actions of procaine resemble those of quinidine. However, the therapeutic value of procaine is limited by rapid enzymatic hydrolysis and prominent adverse effects on the central nervous system (CNS). Procainamide was discovered as a result of a systematic study of congeners and metabolites of procaine to find a compound with clinically useful quinidine-like actions (Mark *et al.*, 1951).

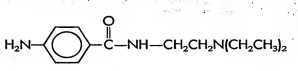
Table 35–6. USEFULNESS OF ANTIARRHYTHMIC DRUGS IN THE TREATMENT OF SPECIFIC CARDIAC ARRHYTHMIAS *

ARRHYTHMIA	CLASS OF ANTIARRHYTHMIC DRUG					
	I_A	I_B	I_C	*II*	*III*	*IV*
Supraventricular						
Atrial fibrillation, conversion	2	0	—	1	1	1
Atrial fibrillation, prophylaxis	3	0	—	2	0	2
Atrial fibrillation, rate control	0	0	—	2	2	2
Paroxysmal supraventricular tachycardia	2	1	NI	3	NI	3
Atrial premature depolarizations	2	1	NI	2	NI	2
Ventricular						
Ventricular premature depolarizations	3	2	NI	2	NI	0
Ventricular tachycardia (unsustained)	3	2	NI	1	NI	0
Ventricular tachycardia (sustained)	3	2	2	1	1, 2 †	0
Digitalis-induced arrhythmias						
Atrial tachycardia with block	1	3	NI	2	NI	NI
Nonparoxysmal AV junctional tachycardia	1	3	NI	2	NI	NI
Ventricular arrhythmias	1	3	NI	2	NI	NI

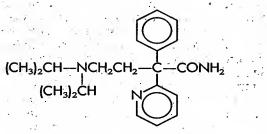
* The utility score is based on an overall estimate of efficacy, convenience, and toxicity. The scale of relative utility is as follows: 0, none; 1, poor; 2, fair; 3, good; 4, excellent; —, insufficient data to give a score; NI, not indicated.
† Depends on the drug (*i.e.*, bretylium, 1, amiodarone 2).

The propensity of procainamide to produce a syndrome similar to systemic lupus erythematosus has encouraged the search for other agents with quinidine-like properties. Disopyramide was introduced in 1978, but it has significant antimuscarinic and negative inotropic actions. Moricizine, developed in the Soviet Union in the 1960s, is the most recent candidate; it is currently under clinical investigation.

Chemistry. The chemistry of the cinchona alkaloids is presented in the discussion of quinine (Chapter 41). Quinidine differs from quinine only in the steric configuration of the secondary alcohol group. Procainamide differs from procaine merely by the replacement of an amide for an ester linkage. The structures of procainamide, disopyramide, and moricizine (a phenothiazine) are as follows:



Procainamide



Disopyramide

Moricizine

Cardiac Electrophysiological Effects. Antiarrhythmic agents in class I_A have powerful direct effects on most types of cells in the heart. Depending on the agent, the electrical properties of cardiac cells are also influenced indirectly by drug-induced alterations of autonomic regulation of the heart.

Automaticity. Although all the drugs in class I_A can cause severe depression of the sinus node in patients with the sick sinus syndrome (*see* Bigger and Reiffel, 1979), only disopyramide appreciably slows the denervated human heart. In normal man, quinidine can increase the sinus rate by cholinergic blockade or by reflexly increasing sympathetic activity; disopyramide usually causes little change in the sinus rate, apparently because its direct depressant effects are counterbalanced by its prominent anticholinergic actions. Therapeutic concentrations of quinidine, procainamide, and disopyramide substantially decrease the firing rate of cardiac Purkinje fibers by a direct action; they decrease the slope of phase-4 depolarization and shift the threshold voltage toward zero. The shift in threshold is due to use-dependent blockade of fast Na^+ channels and slowing of their rate of reactivation. The decrease in the slope of phase 4 has not yet been explained. This effect on the normal automaticity in the His–Purkinje system presents a hazard in the treatment of arrhythmias in the presence of AV block. Therapeutic concentrations of Class I_A agents have little effect on abnormal automaticity in markedly depolarized Purkinje fibers or on delayed afterdepolarizations. However, these agents may prevent triggered activity by preventing the premature depolarization that initiates the process or by shifting the threshold potential in a positive direction.

Excitability, Responsiveness, and Conduction. Class-I_A drugs increase the diastolic electrical current threshold in atrial and ventricular muscle and in Purkinje fibers; they also increase the fibrillation threshold in atria and ventricles. The amplitude, overshoot, and $\dot{V}_{max}$ of phase 0 in atrial, ventricular, and Purkinje cells is decreased in a dose-dependent fashion; however, these effects are not accompanied by a significant change in the resting *Vm*. The upstroke of premature responses is particularly depressed because the drugs cause changes in the voltage and time dependence of reactivation; for any steady-state value of *Vm*, $\dot{V}_{max}$ is reduced and, during dynamic changes in *Vm*, $\dot{V}_{max}$ takes longer to reach its steady-state value (*see* Figure 35–2). The time-dependent changes are most marked at low (less negative) values of *Vm*.

Duration of the Action Potential and Refractoriness. Quinidine, procainamide, and disopyramide cause small but significant increases in the duration of the action potential of ordinary atrial, ventricular, or

Purkinje cells. The effective refractory period (ERP) of these cell types increases much more than would be expected from the changes in the duration of the action potential because of the changes in responsiveness discussed above. By contrast, moricizine shortens the duration of action potentials in Purkinje fibers (*see* Symposium, 1987).

Effect on Reentrant Arrhythmias. Reentrant arrhythmias are abolished by class I_A agents because of their effects on ERP, responsiveness, and conduction. For example, when ventricular premature depolarizations are caused by reentry in loops of Purkinje fibers, one-way block can be converted to two-way block, thus making reentry impossible (*see* Figure 35–4).

The mechanisms of the antiarrhythmic actions of these drugs in atrial flutter or fibrillation are more complex.

Atrial Flutter. Prolongation of the ERP of the atrium is commonly cited as the one desirable attribute of an "antiflutter" drug. The situation is by no means simple, for the effects of antiarrhythmic drugs on ERP and on conduction velocity are inextricably linked. When quinidine or procainamide is administered to a dog in which a circus-movement flutter has been established, or to a patient with atrial flutter, the frequency invariably declines before reversion to sinus rhythm abruptly ensues. Conduction velocity slows in atrial muscle, which could account for the reduction of rate; but the atrial refractory period is also increased, which could reduce the rate by forcing the circulating impulse to travel in relatively refractory tissue. The two actions are opposed. If the predominant effect were a primary reduction of conduction velocity, reversion to sinus rhythm would not be expected to occur until the flutter frequency diminished to less than the prevailing rate of the sinus node. But if the action is primarily on the ERP, then the conduction velocity will be secondarily depressed until some minimal value is reached below which successful impulse propagation is no longer possible. This may well be the mechanism of action of class I_A agents in the experimental situation, but the details of the process are still not clearly defined.

Atrial Fibrillation. If atrial fibrillation were due to a single circus movement about an obstacle so limited in size that activation of the surrounding tissue is irregular and fractionated, then the circuit itself would be unstable. This mechanism seems unlikely, for fibrillation can be, and often is, a very stable arrhythmia. However, if fibrillation is due to the random reentry of numerous fractionated wavelets, changing in breadth, direction, and number from moment to moment, then the persistence of the arrhythmia is critically related to the mass and degree of inhomogeneity of the tissue and to the mean ERP. Vagal stimulation or cholinomimetic drugs should tend to perpetuate the arrhythmia by reducing the mean ERP and by increasing the range of variation of the ERPs. The action of quinidine or disopyramide here is twofold. By virtue of their direct and antivagal actions, they may increase the mean ERP and also reduce the inhomogeneity. Thus, the ability to reduce the number of wavelets possible in a given mass of tissue may be more important than the ability to snuff out a dominant circus movement.

Electrocardiographic Effects. At therapeutic concentrations in man, the agents in class I_A produce no change or only small increases in heart rate and in the P–R, H–V, and QRS intervals. The effects on the A–H interval are variable; quinidine is more apt to shorten this interval (and to increase heart rate) because of its effects on the autonomic regulation of the heart. Although moricizine shortens the Q–T interval, the other agents prolong the Q–T interval, reflecting more rapid and slowed rates of repolarization, respectively. Widening of the QRS complex is related to the plasma concentration of drug, and this effect is sometimes useful for monitoring therapy.

Autonomic Nervous System Effects. In experiments with animals, quinidine has a significant atropine-like action, blocking the effects of vagal stimulation or acetylcholine. Quinidine also has α-adrenergic blocking properties. This action can cause vasodilatation and, via baroreceptors, activate sympathetic efferent activity. Together, the cholinergic blockade and increased β-adrenergic activity caused by quinidine can increase sinus rate and enhance AV nodal conduction in some human subjects.

The anticholinergic action of procainamide is much weaker than that of quinidine. Procainamide does not produce α-adrenergic blockade, but, in dogs, it can block autonomic ganglia weakly and cause a measurable impairment of cardiovascular reflexes.

Disopyramide has cholinergic blocking properties about 10% as potent as atropine (Birkhead and Vaughan Williams, 1977; Mirro *et al.*, 1980). These properties usually nullify its direct depressant effects on the sinus and AV nodes. The drug is neither an α- nor a β-adrenergic antagonist.

Absorption, Distribution, and Elimination. *Quinidine.* When administered orally, quinidine sulfate is absorbed rapidly and peak concentrations in plasma are attained in 60 to 90 minutes. The absorption of quinidine gluconate is slower and perhaps less complete; peak concentrations in plasma are not reached until 3 or 4 hours after an oral dose. Although quinidine can be given intramuscularly, it causes pain at the injection site and a substantial increase in creatine kinase activity in plasma.

About 90% of quinidine in plasma is bound to proteins (α_1-acid glycoprotein and albumin). The drug is distributed rapidly to most tissues except brain, and the apparent volume of distribution is 2 to 3 liters per kilogram.

Quinidine is largely metabolized by the liver, and the metabolites and some of the parent drug (20%) are excreted in the urine; the elimination half-time is about 6 hours. Most urinary metabolites are hydroxylated at only one site, either on the quinoline ring or on the quinuclidine ring; small amounts of dihydroxy compounds are also found. The fraction of a dose of quinidine that is metabolized and the metabolic pathway appear to vary considerably from patient to patient. There is controversy about whether the concentration of quinidine in plasma rises in patients with renal failure or congestive heart failure (*see* Kessler *et al.*, 1974; Conrad *et al.*, 1977; Drayer *et al.*, 1977). The situation is complicated by the fact that some of quinidine's major metabolites are probably cardioactive.

Quinidine is both filtered at the glomerulus and secreted by the proximal renal tubule. Since quinidine is a weak base, its reabsorption is reduced and its excretion is enhanced if the urine is acidic. When the urinary pH is increased from the 6–7 range to the 7–8 range, renal clearance of quinidine decreases by as much as 50% and its concentration in the plasma increases. This situation rarely occurs clinically unless the patient takes sodium bicarbonate or acetazolamide concurrently or has renal tubular acidosis.

Procainamide. Procainamide is quickly and nearly completely absorbed after oral administration to normal subjects. The peak concentration in plasma is reached 45 to 75 minutes after ingestion of capsules, but somewhat later after administration of tablets. In the first week after acute myocardial infarction, oral absorption may be poor, the peak plasma concentration may be quite delayed, and concentrations of the drug may be inadequate to control arrhythmias. Sustained-release formulations of procainamide can increase the duration of action to about 8 hours or more, but these have lower bioavailability than do standard capsules.

About 20% of the procainamide in plasma is bound to proteins. Procainamide is rapidly distributed into most body tissues except the brain, and the apparent volume of distribution is about 2 liters per kilogram. However, this value can decrease substantially in patients with cardiac failure or shock. Compensation for this change should be made in calculating dosage.

Procainamide is eliminated by renal excretion and hepatic metabolism. The major metabolic pathway involves N-acetylation by a bimodally distributed N-acetyltransferase that metabolizes isoniazid, dapsone, and other drugs (Gibson *et al.*, 1975; Reidenberg *et al.*, 1975). However, there is another acetylase system that does not show such genetic variation and that also may contribute to the metabolism of procainamide (Giardina *et al.*, 1977). In fast acetylators or in renal insufficiency, 40% or more of a dose of procainamide may be excreted as N-acetylprocainamide (NAPA), and concentrations of NAPA in plasma may equal or exceed those of the parent drug. This compound, which has been assigned the nonproprietary name of *acecainide*, is a less potent antiarrhythmic agent than procainamide, and has qualitatively different cardiac actions. Although it also prolongs the duration of action potentials in Purkinje fibers, NAPA has little effect on $\dot{V}_{max}$ or automaticity. Hence, information should be available about the concentrations of both procainamide and NAPA in plasma for optimal case management.

Up to 70% of a dose of procainamide is eliminated unchanged in the urine. Procainamide is a weak base that is filtered, secreted by the proximal tubule, and reabsorbed by the distal tubule. Marked increases in the pH of the urine cause a de-

crease in the renal excretion of procainamide. When intrinsic renal function or renal perfusion decreases, the concentration of procainamide in plasma rises significantly. However, as the blood urea nitrogen rises, the fraction of a dose of procainamide that is excreted unchanged decreases, and NAPA can accumulate to dangerous levels.

Disopyramide. About 90% of an oral dose of disopyramide is absorbed, of which a small fraction is subject to first-pass metabolism by the liver. Concentrations in plasma peak at 1 to 2 hours after a dose. At normal therapeutic concentrations (3 μg/ml) about 70% of disopyramide is bound to plasma proteins; the bound fraction varies inversely with the total concentration of drug in plasma. The apparent volume of distribution of disopyramide is about 0.6 liter per kilogram, but the value is dependent on dose because of the saturable binding to plasma protein.

About 50% of a dose of disopyramide is excreted by the kidney unchanged, 20% as the mono-N-dealkylated metabolite, and another 10% as unidentified metabolites. The monodealkylated metabolite has less antiarrhythmic and atropine-like activity than does the parent compound. The half-time for elimination is 5 to 7 hours, and this value is markedly prolonged in patients with renal insufficiency (up to 20 hours or more).

Preparations, Dosage, and Routes of Administration. *Quinidine.* For practical purposes, quinidine is only given orally, although it can be administered either intramuscularly or intravenously under special circumstances. The usual oral dose of quinidine sulfate is 200 to 300 mg three or four times a day for patients with premature atrial or ventricular contractions or for maintenance therapy. Higher and/or more frequent doses can be used for limited periods for treatment of paroxysmal ventricular tachycardia. During maintenance therapy, quinidine will usually reach a steady state within about 24 hours, and its concentration in plasma will fluctuate less than 50% between doses. Because of the large interindividual variation, drug interactions, and other causes of variability, it is wise to examine the ECG carefully after the initial dose of quinidine and to measure the plasma concentration of the drug at steady state (*see* Appendix II). Adjustment of dosage is often necessary.

Quinidine sulfate (CIN-QUIN) is available in tablets (100 to 300 mg) and capsules (200 and 300 mg); 300-mg sustained-release tablets (QUINIDEX) are available, as is an injection (200 mg/ml). Preparations of the gluconate and polygalacturonate salts are also marketed.

Procainamide. Procainamide hydrochloride (PRONESTYL, others) is available for oral administration as capsules and tablets (250 to 500 mg) and as sustained-release tablets (250 to 1000 mg). *Procainamide hydrochloride injection* contains 100 or 500 mg/ml and is suitable for intramuscular and intravenous injection.

Procainamide can be administered intravenously, intramuscularly, or orally. The concentration in plasma needed to produce antiarrhythmic effects is usually 3 to 10 μg/ml, and occasionally is much higher. The probability of toxicity becomes greater as the plasma concentration rises above 8 μg/ml. The cardiac effects of procainamide are enhanced if the concentration of K^+ in plasma is elevated.

In acute or unstable situations, intravenous administration of procainamide is desirable for speed (injection or rapid infusion), precision (constant infusion), and reliability of effect. The total loading dose is never given as a single intravenous injection because it can cause hypotension. One rapid and safe method to establish effective concentrations in plasma is intermittent intravenous administration: 100 mg is injected over 2 to 4 minutes, and this dose is repeated every 5 minutes until the arrhythmia is controlled, until adverse effects are seen, or until the total size of the dose (about 1000 mg) suggests that the arrhythmia under treatment is resistant. The 5-minute dosing interval permits examination of the blood pressure and ECG after each dose. Serious hypotension or excessive widening of the QRS interval can thus be avoided. Alternatively, the same dose can be given over a similar period by rapid intravenous infusion. For example, 600 mg can be infused at a rate of 20 mg per minute. The same precautions should be taken. When the arrhythmia is controlled, a constant-rate intravenous infusion is often used to maintain effective concentrations in plasma. The infusion rate can be estimated as the product of the desired concentration (3 to 10 μg/ml) and the estimated total clearance of procainamide (*see* Appendix II).

For long-term oral therapy, total daily doses of 3 to 6 g or more usually are required for therapeutic efficacy. Because its elimination half-life is short (about 3 hours in normal subjects and up to 5 to 8 hours in patients with cardiac disease), the drug must be given fairly frequently. However, most patients can take procainamide orally at intervals of 6 to 8 hours. A steady state is reached within 1 day without loading doses because of the short half-life of the drug. When changing from intravenous infusion to oral dosage, the infusion should be stopped and about one elimination half-time permitted to elapse before administration of the first oral dose; the oral dose can be chosen very precisely based on the previous intravenous dose and the resulting plasma concentrations.

Disopyramide. In the United States, disopyramide is approved only for oral administration. It is available as *disopyramide phosphate* in immediate- or controlled-release capsules containing 100 or 150 mg of the base (NAPAMIDE, NORPACE). The

usual total daily dose is 400 to 800 mg. This amount can be divided into four doses (most often 100 to 150 mg four times daily) alternatively, 200 to 300 mg of a controlled-release preparation can be given every 12 hours. Although loading doses of 200 to 300 mg will rapidly produce effective concentrations, loading doses are not given to patients with cardiomyopathy or possible cardiac decompensation, and initial doses are limited to 100 mg every 6 to 8 hours. Therapy is never initiated with a controlled-release preparation. Maintenance doses must be carefully adjusted for patients with renal failure according to the creatinine clearance; efficacy, toxic manifestations, and plasma concentrations should be monitored in such patients.

Therapeutic Uses. The drugs in class I_A have a broad spectrum of action and are effective for short- and long-term treatment of supraventricular and ventricular arrhythmias. Although experience in Europe indicates that disopyramide is useful in the treatment of atrial arrhythmias, in the United States it is approved only for the treatment of ventricular arrhythmias in adults. Individualization of dosage is usually required at the outset of therapy because both plasma concentrations and antiarrhythmic responses will vary from patient to patient. Several 24-hour Holter ECG recordings are often required to ensure adequate control of arrhythmias. Vigilance must be maintained to detect toxic reactions.

Paroxysmal Supraventricular Tachycardia (PSVT). Quinidine, procainamide, and disopyramide can be effective against recurrent, aggravating PSVT, either the usual AV nodal reciprocating tachycardia or the PSVT seen in the Wolff–Parkinson–White syndrome. In the AV nodal form of PSVT, digitalis administration and other methods usually are tried before quinidine or other drugs in class I_A. The mode of action of these agents in PSVT is not certain. They may suppress the atrial premature depolarizations that trigger the PSVT, or alter conduction and refractoriness of the atrium and AV node so that PSVT no longer occurs. In the Wolff–Parkinson–White syndrome, these drugs slow conduction and increase refractoriness in the accessory AV connection and, therefore, prevent attacks of PSVT.

Atrial Flutter or Fibrillation. Quinidine was once used as the drug of choice for conversion of atrial flutter or atrial fibrillation to sinus rhythm. Since the advent of direct-current (DC) cardioversion, quinidine and procainamide have been relegated to supporting roles in the management of these two arrhythmias. Patients scheduled for cardioversion are given oral maintenance doses 1 or 2 days before the anticipated cardioversion. Perhaps one third of patients with atrial fibrillation and a similar proportion of patients with atrial flutter will convert to sinus rhythm before cardioversion, but the majority require DC shock. Maintenance therapy with quinidine or procainamide helps to prevent recurrence of atrial fibrillation. If atrial premature depolarizations occur soon after cardioversion, the dose of drug should be increased until they are abolished or drug toxicity is encountered. If uninterrupted sinus rhythm resumes after cardioversion, the concentration of drug in plasma should be adjusted to achieve optimal steady-state values (*e.g.*, between 2 and 5 μg of quinidine per milliliter).

Ventricular Premature Depolarizations and Unsustained Ventricular Tachycardia. Class-I_A drugs are effective for the long-term treatment of these arrhythmias or for the the prevention of ventricular fibrillation. Ventricular premature depolarization (VPD) is a very common rhythm disturbance. VPDs are treated when they cause discomfort (palpitations), impair hemodynamic performance, or increase the likelihood of death (*see* Table 35–2). When treating VPDs or brief recurrent bursts of ventricular tachycardia, the dosage of drug is adjusted and 24-hour Holter ECG recordings are used to establish drug efficacy. Usually, the dosage of drug is increased until complex forms (pairs or runs of VPDs) are abolished and the frequency of VPDs is reduced by 70 to 80%; this dosage is then maintained. When the arrhythmia is caused by an acute process, such as open-heart surgery, acute myocardial infarction, or acute myocarditis, the drug can be discontinued when the situation is resolved. If the arrhythmia treated was life threatening, the drug should be discontinued while the patient is being monitored.

Sustained Ventricular Tachycardia. The treatment of sustained ventricular tachycardia is quite different. Prior to the advent of DC cardioversion, heroic and skilled dosage with quinidine was used to convert ventricular tachycardia to sinus rhythm. The incidence of toxicity was high with this approach, and it has been abandoned. Although sustained ventricular tachycardia can be relatively resistant to treatment with drugs, it usually responds readily to DC conversion. After conversion, drug efficacy is evaluated by electrophysiological observations (Horowitz *et al.*, 1980; Swerdlow *et al.*, 1983).

Digitalis-Induced Arrhythmias. The complex rhythm disturbances that can attend digitalis toxicity are discussed in detail in Chapter 34. Although quinidine or other class I_A agents can be effective for the treatment of digitalis-induced arrhythmias, they are not the preferred drugs, because adverse effects on cardiac rhythm are more likely to occur with their use than with other effective treatments (*e.g.*, phenytoin, lidocaine, or anti-digoxin antibody).

Untoward Effects. *Quinidine.* About one third of the patients who receive quinidine will have immediate adverse effects that necessitate discontinuation of therapy.

If this initial hurdle is passed, few extracardiac adverse effects are encountered during long-term therapy. However, excessive concentration of the drug in plasma will cause adverse effects in any patient. Because quinidine has a low therapeutic ratio, constant vigilance is required in every patient taking this drug (*see* Woosley and Roden, 1987).

Cardiotoxicity. As the concentration of quinidine in plasma rises above 2 μg/ml, the QRS complex and the Q–T_c interval will widen progressively. These changes are useful in monitoring quinidine therapy. If the duration of the QRS complex increases by 50% or more, the dosage should be reduced. At high plasma concentrations of the drug, cardiac toxicity may become severe; SA block or arrest, high-grade AV block, ventricular tachyarrhythmias, or asystole may occur. Conduction is slowed tremendously in all parts of the heart. In addition, Purkinje fibers can become depolarized and develop abnormal automaticity. These changes are responsible for the bizarre arrhythmias seen in severe poisoning with quinidine. Quinidine can produce early afterdepolarizations and triggered activity in Purkinje fibers exposed to low concentrations of K^+ *in vitro* (Roden and Hoffman, 1985). Polymorphic ventricular tachycardia (*torsades de pointes*) caused by quinidine is a life-threatening event and must be treated with the utmost caution. The ECG must be closely monitored in an intensive care unit. Sodium lactate or bicarbonate, catecholamines, glucagon, and magnesium sulfate may be useful in counteracting ventricular tachyarrhythmias caused by quinidine. Quinidine and its hydroxy metabolites can be removed by dialysis (Conrad *et al.*, 1977).

Occasionally, patients taking quinidine experience syncope or sudden death. In some instances, this reaction may be the result of high concentrations of quinidine in plasma or the result of coexisting digitalis toxicity. However, *torsades de pointes* may occur in susceptible individuals while the concentrations of quinidine in plasma are below or within the therapeutic range. Individuals with the long Q–T syndrome or those who respond to low concentrations of quinidine with marked lengthening of the Q–T interval appear to be particularly at risk and should not be treated with this drug (Koster and Wellens, 1976). Bradycardia and hypokalemia are also risk factors for *torsades de pointes* (Morganroth, 1987).

A frequently mentioned complication of quinidine when the drug is used to treat atrial fibrillation is the so-called paradoxical increase in ventricular rate. Quinidine and other drugs in class I_A can cause a substantial decrease in the atrial rate in atrial fibrillation. If the atrial rate decreases sufficiently, the ventricular rate may increase abruptly because of the decrease in concealed conduction of atrial impulses in the AV node. In some patients, quinidine (or disopyramide) may be anticholinergic as well. A paradoxical increase in ventricular rate is not common in patients treated with these drugs. However, the effect can be so dramatic that it is traditional to digitalize patients with atrial fibrillation or flutter prior to administration of a class-I_A antiarrhythmic agent.

Blood Pressure. Quinidine can cause significant hypotension, particularly when given intravenously. This response is probably due to the α-adrenergic blocking effect of the drug. Hemodynamic studies indicate that hypotension due to quinidine is caused by vasodilatation without a significant decrease in cardiac output; therapeutic concentrations of quinidine have no significant adverse effects on myocardial performance.

Arterial Embolism. The risk of embolism after conversion of atrial fibrillation to sinus rhythm is a source of concern. The fibrillating atria do not contract, and thrombi often develop in the left atrium. After sinus rhythm resumes, atrial contraction may dislodge thrombi; stroke is the most dreaded sequela of the resultant arterial embolization. However, the long-term risk of systemic embolization is greater if atrial fibrillation persists than if conversion to sinus rhythm occurs. If cardioversion is performed as an elective procedure, patients are usually given anticoagulants for 1 to 2 weeks prior to conversion.

Cinchonism. Like other cinchona alkaloids and the salicylates, quinidine can cause cinchonism. Symptoms of mild cinchonism include tinnitus, loss of hearing, slight blurring of vision, and gastrointesti-

nal upset. If toxicity is severe, headache, diplopia, photophobia, and altered color perception may occur, as can confusion, delirium, and psychosis. The skin may be hot and flushed; nausea, vomiting, diarrhea, and abdominal pain are likely.

Gastrointestinal Symptoms. The most common adverse reactions to quinidine occur in the gastrointestinal tract—nausea, vomiting, and diarrhea. Gastrointestinal symptoms often occur even when drug concentrations in plasma are low. This type of adverse reaction is apparent almost immediately after quinidine is started and forces early discontinuation of the drug in almost one third of patients so treated.

Hypersensitivity Reactions. Hypersensitivity to quinidine can cause fever; this reaction is rare and disappears when the drug is discontinued. Rarely, quinidine causes anaphylactic reactions, which require emergency measures. Thrombocytopenia is an uncommon but potentially lethal outcome of treatment with quinidine. Thrombocytopenia usually occurs after several weeks or months of therapy and is due to formation of drug–platelet complexes that evoke a circulating antibody. When quinidine, platelets, antibody, and complement are all present in the circulation, platelets agglutinate and lyse. Thrombocytopenia can be profound, and severe bleeding may ensue. If quinidine is stopped, the platelet count will return to near normal within days. Until the bleeding time is normal, patients should be kept in the hospital and, if necessary, treated with adrenocorticosteroids. Asthma-like respiratory difficulty or vascular collapse can occur as a result of hypersensitivity. Artificial ventilation and supportive measures are usually effective.

Procainamide. Cardiotoxicity. Excessive plasma concentrations of procainamide produce ECG changes very similar to those seen during quinidine therapy. The same rules and precautions for using and discontinuing quinidine (*see* above) pertain to procainamide. Interestingly, the syndrome of marked Q–T prolongation and *torsades de pointes* described for quinidine is less common with procainamide and usually occurs in renal failure when plasma concentrations of NAPA rise markedly. Procainamide, like quinidine, will slow the atria in atrial fibrillation and can thereby cause a "paradoxical" increase in the ventricular response.

Blood Pressure. If procainamide is administered intravenously, it can cause hypotension. Intermittent or continuous intravenous infusion can be adjusted so that significant hypotension is unusual, provided that doses do not exceed 600 mg over a period of 25 to 30 minutes. Toxic concentrations of procainamide can diminish myocardial performance and promote hypotension.

Extracardiac Adverse Effects. During oral administration of procainamide, gastrointestinal symptoms (anorexia, nausea, vomiting, and, rarely, diarrhea) may occur; these symptoms are much less common than with quinidine. Procainamide can produce adverse effects on the CNS, including giddiness, psychosis, hallucinations, and mental depression.

Hypersensitivity Reactions. Occasionally, fever occurs during the first few days of therapy and forces discontinuance of procainamide. Agranulocytosis may occur in the early weeks of therapy; fatal infections may follow (Meyers *et al.*, 1985). Leukocyte and differential blood counts should be done regularly during therapy, and complaints of sore throat should be promptly evaluated. Myalgias, angioedema, skin rashes, digital vasculitis, and Raynaud's phenomenon have all been attributed to procainamide.

Procainamide can cause a syndrome that superficially resembles authentic systemic lupus erythematosus (SLE). Arthralgia is the most common symptom; pericarditis, pleuropneumonic involvement, fever, and hepatomegaly are common signs. The most serious complication is hemorrhagic pericardial effusion with tamponade. Drug-induced SLE is different from the naturally occurring disease in that there is no predilection for females; the brain and kidney are spared; leukopenia, anemia, thrombocytopenia, and hyperglobulinemia are rare; and false-positive serologic tests for syphilis do not occur. The drug-induced syndrome is reversible when procainamide is discontinued. At least 60 to 70% of patients who receive procainamide will develop an-

tinuclear antibodies after 1 to 12 months of therapy. These antibodies are directed against nuclear histones. Only 20 to 30% of patients with antinuclear antibodies will develop the clinical symptoms and signs of the SLE syndrome if treatment is continued. When symptoms occur, LE-cell preparations are often positive. The development of antinuclear antibodies alone is insufficient reason to discontinue therapy with procainamide. However, the benefits and risks of continued therapy should be assessed, and procainamide is usually stopped when patients become symptomatic. It is not yet clear if individuals who acetylate procainamide slowly have an increased risk of developing the SLE-like syndrome; however, antinuclear antibodies appear more rapidly in slow acetylators than in fast acetylators (Giardina *et al.*, 1977; Woosley *et al.*, 1978). The use of acecainide (NAPA) has only rarely been associated with the development of antinuclear antibodies.

Disopyramide. The anticholinergic action of disopyramide produces a significant incidence of dry mouth, constipation, blurred vision, urinary hesitancy, and, occasionally, urinary retention. These effects are more common than with other drugs in class I_A. Disopyramide can cause nausea, abdominal pain, vomiting, or diarrhea, but gastrointestinal symptoms are significantly less common than when quinidine is used. Disopyramide reduces cardiac output and left ventricular performance by a direct depressant effect and peripheral arteriolar constriction. The adverse effects on ventricular function can be striking in patients who have preexisting ventricular failure (Jensen *et al.*, 1975; Podrid *et al.*, 1980). Great caution should be exercised in treating such patients with disopyramide. The adverse hemodynamic effects are more marked than those of other antiarrhythmic drugs. The blood pressure usually increases transiently after intravenous administration of disopyramide, even though the cardiac output falls; total peripheral vascular resistance thus increases markedly (*see* Di Bianco *et al.*, 1987; Willis, 1987).

Drug Interactions. Drugs that induce drug-metabolizing enzymes in the liver, such as phenobarbital or phenytoin, may significantly shorten the duration of action of quinidine by increasing its rate of elimination. Since patients vary tremendously in their susceptibility to enzyme induction, it is difficult to predict which individuals will be affected. When quinidine is given to patients who have stable concentrations of digoxin in plasma, the digoxin concentration usually doubles because of a decrease in its clearance (Bigger, 1982). Occasionally, patients who are receiving warfarin or other oral anticoagulants will have an increase in prothrombin time after quinidine is begun; the mechanism of this reaction is not clear. Since quinidine is an α-adrenergic blocking agent, it can interact additively with drugs that cause vasodilatation or decreased blood volume. For example, nitroglycerin can cause severe postural hypotension in patients who are taking quinidine. The effect of any given concentration of any antiarrhythmic drug in class I_A on conduction in the heart is greater when the concentration of K^+ in plasma is increased.

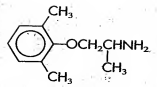
Class I_B: Lidocaine, Phenytoin, Tocainide, and Mexiletine

Antiarrhythmic drugs in class I_B produce only small changes in phase-0 depolarization and conduction velocity in myocardial Purkinje fibers when resting values of *Vm* are normal (*see* Table 35–3). However, the depressant effects of class-I_B drugs on these parameters are markedly intensified when the membrane is depolarized or when the frequency of excitation is increased. In contrast to drugs in class I_A, those in class I_B usually hasten membrane repolarization. Lidocaine is the prototypical agent, although it is the only member of this class that is not effective orally.

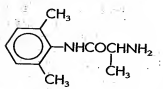
History. Lidocaine is widely used as a local anesthetic (*see* Chapter 15). It was introduced as an antiarrhythmic agent in 1962 for the emergency treatment of ventricular arrhythmias after cardiac surgery or acute myocardial infarction. Two orally effective relatives of lidocaine have recently become available—tocainide in 1984 and mexiletine in 1986.

Phenytoin has been used since 1938 for the treatment of seizures (*see* Chapter 19). In 1950, Harris and Kokernot found that phenytoin was therapeutically effective for ventricular tachycardia in experimental myocardial infarction in dogs. Clinical studies have demonstrated its usefulness for ventricular arrhythmias in man, especially those associated with digitalis toxicity.

Chemistry. The chemistry and structures of lidocaine and phenytoin are discussed in Chapters 15 and 19, respectively. The chemical structures of tocainide and mexiletine closely resemble that of lidocaine and are as follows:



Mexiletine



Tocainide

Cardiac Electrophysiological Effects. *Automaticity.* It is distinctly unusual for therapeutic concentrations of class-I_B drugs to depress the human sinus node, but it can occur in patients with preexisting disease of the sinus node (Bigger and Reiffel, 1979; Kerr *et al.*, 1983). Therapeutic concentrations of these agents decrease the slope of normal phase-4 depolarization in Purkinje fibers. This action is caused by a decrease in the pacemaker current (i_f) and an increase in time-independent outward current (i_{K_1}) (Weld and Bigger, 1976; Carmeliet and Saikawa, 1982). However, the capacity of tocainide and mexiletine to reduce the automaticity of Purkinje fibers is more reminiscent of quinidine, in that a shift of the threshold voltage for firing toward more positive values of *Vm* has an important role (Roden and Woosley, 1986b; Campbell, 1987). Lidocaine also can counteract automaticity in depolarized, stretched Purkinje fibers, and both lidocaine and phenytoin are effective in abolishing triggered activity due to digitalis-induced delayed afterdepolarizations (Rosen *et al.*, 1976; Peon *et al.*, 1978). These effects could result from an increase in i_{K_1} that overcomes small inward currents that cause depolarization or from a decrease in inward Na^+ current (Carmeliet and Saikawa, 1982; Colatsky, 1982).

Excitability and Threshold. Class-I_B agents cause an increase in the diastolic electrical current threshold in cardiac Purkinje fibers by increasing K^+ conductance (g_{K_1}) without changing resting *Vm* or the voltage threshold. They also increase the threshold for ventricular fibrillation.

Responsiveness and Conduction. The effects of lidocaine on membrane responsiveness are complex. The steady-state relationship between $\dot{V}_{max}$ and *Vm* is little altered in normal Purkinje fibers by therapeutic concentrations of lidocaine, but fast responses are prevented at low (less negative) values of *Vm*. This effect can be explained by a lidocaine-induced increase in i_{K_1}. The effect of lidocaine on responsiveness depends on $[K]_o$: at $[K]_o$ up to 4.5 mM, therapeutic concentrations have little effect; at $[K]_o$ of 5.6 or 6.0, therapeutic concentrations of lidocaine reduce $\dot{V}_{max}$ at any level of *Vm* (Obayashi *et al.*, 1975). Toxic concentrations shift responsiveness in much the same way as quinidine does. Lidocaine suppresses the responsiveness of abnormal ventricular muscle fibers that survive experimental infarction (Kupersmith *et al.*, 1975). The effect of lidocaine on responsiveness is use dependent and is increased at fast heart rates (*see* above) (Hondeghem and Katzung, 1980; Bean *et al.*, 1983).

Because of the large safety factor for conduction, lidocaine and the other drugs in class I_B usually have no effect on conduction velocity in normal tissues of the His–Purkinje system or ventricular muscle. Under abnormal circumstances, these agents may either decrease or increase conduction velocity in the His–Purkinje system or in ventricular muscle; in ischemic tissues, conduction velocity usually decreases substantially (Kupersmith *et al.*, 1975). In tissues depolarized by stretch or low $[K]_o$, lidocaine can cause hyperpolarization and significant increases in conduction velocity (Arnsdorf and Bigger, 1972). It is not known if other drugs in class I_B share this property with lidocaine.

Duration of the Action Potential and Refractoriness. Antiarrhythmic drugs in class I_B cause almost no change in the duration of the action potential of atrial fibers. They substantially decrease the duration of the action potential in Purkinje fibers and ventricular muscle; this effect is attributed to blockade of small Na^+ currents that flow during the plateau of the action potential (Colatsky, 1982). The greatest change is seen in the portions of the His–Purkinje system in which the duration of the action

potential is normally longest (Wittig *et al.*, 1973). This tends to reduce the temporal and spatial dispersion of refractoriness. The effective refractory period shortens after exposure to drugs in this class.

Effect on Reentrant Arrhythmias. Class-I_B drugs can abolish ventricular reentry, either by causing two-way block or by improving conduction. If one-way block occurs in ischemic, depolarized elements of a reentry circuit, two-way block is the more likely mechanism. In patients with impaired AV nodal and ventricular conduction, tocainide and mexiletine may be more apt to reduce conduction velocities in the affected regions than is lidocaine (*see* Keefe *et al.*, 1981). Conduction can actually be improved by lidocaine if depolarization and slow conduction are due to decreased g_{K_1} (*e.g.*, stretch or low $[K]_o$).

The drugs in class I_B are much less effective than quinidine, procainamide, or disopyramide in slowing the atrial rate in atrial flutter or atrial fibrillation or in converting these arrhythmias to sinus rhythm. This is expected, since class-I_B agents have so little effect on either refractoriness or responsiveness in the atria.

Electrocardiographic Effects. In striking contrast to the drugs in class I_A, those in class I_B cause negligible change in the ECG; the Q–T interval may shorten, but the QRS does not widen. The refractory period of the AV node shortens or does not change; in patients with atrial flutter and who show substantial shortening of the AV nodal refractory period, a marked increase in ventricular response can result. Usually the ERP in the His–Purkinje system shortens substantially during treatment with these agents; however, it can lengthen in patients with preexisting bundle-branch disease.

Autonomic Nervous System Effects. Except for phenytoin, the agents in class I_B have no significant interaction with the autonomic nervous system. Most of the effects of phenytoin, if not all, arise from actions within the CNS; vagal efferent activity is modulated, and the efferent traffic in cardiac sympathetic nerves that is enhanced during digitalis intoxication is reduced by phenytoin.

Absorption, Distribution, and Elimination. *Lidocaine.* Although lidocaine is well absorbed after oral administration, it is subject to extensive first-pass hepatic metabolism, and only about one third of the drug reaches the general circulation. Many patients experience nausea, vomiting, and abdominal discomfort after oral administration of lidocaine; this route is not used. The drug is almost completely absorbed after intramuscular administration.

About 70% of lidocaine in plasma is bound to proteins, mostly α_1-acid glycoprotein. Distribution is rapid, and the apparent volume of distribution for lidocaine is normally about 1 liter per kilogram; this volume is substantially reduced in patients with heart failure.

Essentially no lidocaine is excreted unchanged in the urine. Deethylation in the liver results in the appearance of monoethylglycylxylidine and then glycine xylidide. The former metabolite has antiarrhythmic activity, while the latter has almost none (Burney *et al.*, 1974). Severe hepatic disease or reduced perfusion of the liver in heart failure decreases the rate of metabolism. The clearance of lidocaine approaches the rate of hepatic blood flow and is thus very sensitive to changes in this parameter (Nies *et al.*, 1976). The clearance of lidocaine also may decrease as a result of prolonged infusion (LeLorier *et al.*, 1977). The half-time for elimination is normally about 100 minutes.

Phenytoin. Only a few points that are crucial to the use of phenytoin as an antiarrhythmic drug will be discussed here. A more detailed discussion is presented in Chapter 19. Absorption of phenytoin from the gastrointestinal tract is slow and somewhat erratic. Absorption after intramuscular injection is also slow and may be incomplete. About 90% of phenytoin in plasma is bound to albumin; the fraction is less in patients with uremia. After intravenous administration, phenytoin is distributed to tissues rapidly. The drug is eliminated by hepatic hydroxylation. The major metabolites of phenytoin probably lack antiarrhythmic activity. Metabolism is relatively slow and is not substantially altered by changes in hepatic blood flow. The enzyme system that metabolizes phenytoin be-

comes saturated by concentrations of the drug in the therapeutic range; hence, the half-time for elimination is dose dependent, and unexpected toxicity can occur (*see* Chapter 19; Appendix II).

Tocainide. Tocainide is completely absorbed after oral administration; peak concentrations in plasma occur within 1 to 2 hours. About 40% of a dose of tocainide is excreted as such in the urine. The half-life in plasma is 11 to 15 hours, and this value may increase twofold in patients with renal or hepatic disease (*see* Holmes *et al.*, 1983; Hasegawa, 1985).

Mexiletine. Mexiletine is readily absorbed after oral administration, and its systemic bioavailability is about 90%. The drug is eliminated after hepatic metabolism; about 10% of a dose is found unchanged in the urine. The elimination half-life is approximately 10 hours (*see* Schrader and Bauman, 1986).

Preparations, Dosage, and Routes of Administration. *Lidocaine. Lidocaine hydrochloride injection* (XYLOCAINE) is available for intravenous administration in solutions for infusion (2, 4, or 8 mg/ml), for direct administration (10 or 20 mg/ml), and for dilution into admixtures (40, 100, or 200 mg/ml); solutions for intramuscular injection contain 100 mg/ml. These solutions contain no preservative, sympathomimetic, or other vasoconstrictor. Catastrophic arrhythmias can occur if preparations that contain sympathomimetic amines are used accidentally.

Lidocaine is only administered intravenously or intramuscularly. To achieve effective concentrations rapidly, intravenous administration of about 0.7 to 1.4 mg/kg of body weight is used. A second injection may be required in 5 minutes; no more than 200 to 300 mg should be given in 1 hour. Smaller doses should be used for patients who have heart failure. Rapid infusion may also be employed to administer a loading dose. A constant rate of intravenous infusion is used to maintain an effective concentration. Infusions in the range of 1 to 4 mg per minute produce therapeutic concentrations in plasma of 1 to 5 μg/ml in 7 to 10 hours; in patients with heart failure or shock, the same rate of infusion will produce plasma concentrations two or more times higher (*see* Appendix II). As the circulatory status changes, hepatic blood flow can change dramatically and shifts in the concentration of lidocaine in plasma will reflect these alterations (Nies *et al.*, 1976). An intramuscular dose of 4 to 5 mg/kg will produce an effective concentration of lidocaine within 15 minutes, and this therapeutic level is maintained for about 90 minutes.

Phenytoin. The preparations of phenytoin are presented in Chapter 19. Phenytoin should be given orally or by intermittent injection; the injectable preparation has a pH of about 12 and causes severe phlebitis if infused. Critical arrhythmias should not be treated by the intramuscular route because absorption is too unreliable. The schedule for intermittent intravenous injection of phenytoin is almost identical to that described above for procainamide: 100 mg of phenytoin is given every 5 minutes until the arrhythmia is controlled or until adverse effects are encountered (Bigger *et al.*, 1968). The rate of injection should not exceed 50 mg per minute. Usually about 700 mg is required; doses above 1000 mg are rarely needed. Oral treatment of arrhythmias usually is initiated with loading doses because of phenytoin's long elimination half-time. A dose of 15 mg/kg is given the first day, 7.5 mg/kg on the second day, and 4 to 6 mg/kg per day for long-term maintenance (most often 300 to 400 mg per day). The oral maintenance dose can be given once a day or divided into two portions.

Tocainide. Tocainide hydrochloride (TONOCARD) is available in 400- and 600-mg tablets. The usual oral dose is 400 to 600 mg every 8 hours up to a maximum of about 2400 mg per day; daily dosages should be reduced to less than 1200 mg in patients with renal or hepatic impairment.

Mexiletine. Mexiletine hydrochloride (MEXITIL) is supplied in 150-, 200-, and 250-mg capsules. The usual oral dosage is 200 to 300 mg (up to a maximum of 400 mg) given every 8 hours with food or antacids. For rapid response, an initial dose of 400 mg may be given. Reduced dosage may be required in patients with hepatic impairment.

Therapeutic Uses. *Lidocaine.* Lidocaine is used almost exclusively to treat ventricular arrhythmias, primarily in intensive care units. Lidocaine is effective against ventricular arrhythmias caused by acute myocardial infarction, open-heart surgery, and digitalis. Lidocaine tends to prevent primary ventricular fibrillation in the acute phase of myocardial infarction, but no beneficial effect on mortality has been demonstrated (DeSilva *et al.*, 1981; MacMahon *et al.*, 1988).

Phenytoin. Phenytoin is used to treat ventricular arrhythmias, paroxysmal atrial flutter or fibrillation, and supraventricular arrhythmias caused by digitalis. Phenytoin is effective against the ventricular arrhythmias seen after open-heart surgery and acute myocardial infarction, but lidocaine is equally effective and is easier to use. Phenytoin is relatively ineffective against recurrent, drug-resistant ventricular tachycardia in patients with chronic ischemic heart disease. Phenytoin reduces ventricular arrhythmias in the year after myocardial infarction if the concentration of the drug in plasma is kept above 10 μg/ml; such concentrations are readily attained with doses of 400 to 500 mg per day. Phenytoin is highly effective against multiform and complex ventricular premature depolarizations, ventricular tachycardia, and atrial tachycardia with AV block induced by digitalis; often, small doses are effective. It is somewhat less effective against nonparoxysmal AV junctional tachycardia; larger doses are needed, and a larger fraction of cases fails to respond. Phenytoin has been used effectively with electro-

physiological guidance against sustained ventricular tachycardia in chronic coronary heart disease and against ventricular tachyarrhythmias in the long Q–T syndrome, in conjunction with a β-adrenergic blocking agent (Schwartz *et al.*, 1975). The effects of phenytoin on sinus arrest or sinoatrial block caused by digitalis in human subjects are unknown. Phenytoin is relatively ineffective against the common atrial arrhythmias, such as atrial flutter, atrial fibrillation, and supraventricular tachycardia (*see* Atkinson and Davison, 1974; Wit *et al.*, 1975).

Tocainide and Mexiletine. Tocainide and mexiletine are indicated for the oral treatment of ventricular arrhythmias; responsiveness to lidocaine is quite predictive of a response to tocainide. Long-term oral treatment of ventricular ectopic beats with either tocainide or mexiletine has met with variable success. The effectiveness of these drugs is less than that of procainamide or quinidine (*see* Holmes *et al.*, 1983). Mexiletine can suppress ventricular tachycardia in some patients who have not responded to quinidine or other drugs in class I_A.

Untoward Effects. Antiarrhythmic agents in class I_B have fewer adverse cardiac effects than do those in either class I_A or class I_C. They cause less serious proarrhythmic effects and are less likely to aggravate heart failure.

Lidocaine. Lidocaine has few undesirable cardiovascular effects. Its main adverse effects are on the CNS. At concentrations in plasma near 5 μg/ml, symptoms are often subtle, such as feelings of dissociation, paresthesias (often perioral), mild drowsiness, or agitation. Higher concentrations may cause decreased hearing, disorientation, muscle twitching, convulsions, or respiratory arrest. The minor CNS effects are not dangerous, but do severely disturb some patients. Such symptoms should prompt a decrease of the infusion rate. The more severe toxic manifestations are life threatening.

Phenytoin. The most prominent adverse effects of phenytoin during short-term treatment of arrhythmias are referable to the CNS and include drowsiness, nystagmus, vertigo, ataxia, and nausea. The progression of such symptoms shows an orderly relationship to increasing concentrations in plasma. In short-term treatment of arrhythmias, neurological signs usually indicate that plasma concentrations are in excess of 20 μg/mL. This information is useful; if an arrhythmia has not responded to phenytoin at concentrations of about 20 μg/ml, it is unlikely to respond at higher concentrations.

Tocainide and Mexiletine. Both tocainide and mexiletine cause CNS symptoms (*e.g.*, dizziness, light-headedness, and tremor) and gastrointestinal symptoms (*e.g.*, nausea, vomiting, and anorexia) (Roden and Woosley, 1986b; Campbell, 1987). The use of tocainide, but not of mexiletine, has been associated with agranulocytosis, bone marrow depression, and thrombocytopenia (Volosin *et al.*, 1985; Soff and Kadin, 1987). The sequelae of granulocytopenia have included serious infections, sepsis, and death. When the white blood cell count is less than 1000, the mortality rate is about 25%. Granulocytopenia usually occurs in the first 12 weeks of treatment; it is recommended that white blood cell, differential, and platelet counts be done weekly for the first 3 months of treatment. If abnormalities are detected, tocainide should be discontinued. The blood cell counts usually return to normal within a month. Because of the risk of agranulocytosis, tocainide should be used only when other drugs have been ineffective.

Drug Interactions. Few drug interactions have been reported with lidocaine. β-Adrenergic antagonists can decrease hepatic blood flow in patients with heart disease, causing a decrease in the rate of hepatic metabolism of lidocaine and an increase in its plasma concentration (Nies *et al.*, 1976). Other basic drugs can displace lidocaine from its binding sites on α_1-acid glycoprotein (Routledge *et al.*, 1980). Plasma concentrations of lidocaine are higher in patients who are receiving cimetidine concurrently. The mechanism of this interaction is complex, but the dose of lidocaine may require adjustment (Knapp *et al.*, 1983). Lidocaine can potentiate the effects of succinylcholine.

The hepatic metabolism of mexiletine can be accelerated by concurrent administration of phenytoin or rifampin. No clinically significant drug interactions have been reported for tocainide.

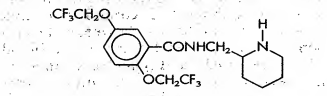
A large number of interactions with other drugs have been described during long-term administration of phenytoin; these are discussed in Chapter 19.

Class I_C: Flecainide, Encainide, and Propafenone

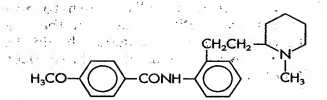
Class-I_C drugs have a high affinity for sarcolemmal Na^+ channels; they are the most potent of the antiarrhythmic agents in

slowing conduction of the cardiac impulse and in suppressing i_{Na} and spontaneous ventricular premature complexes (*see* Symposium, 1984c; Roden and Woosley, 1986a). The first drug in this class, flecainide, was introduced into clinical practice in the United States in 1986. Encainide is also available for general use, while propafenone and indecainide are being investigated. The role of these drugs in the treatment of supraventricular and ventricular arrhythmias is still being defined.

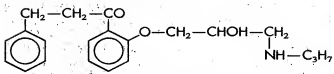
Chemistry. The structural formulas of flecainide, encainide, propafenone, and indecainide are as follows:



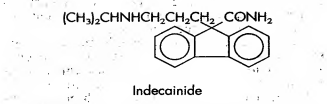
Flecainide



Encainide



Propafenone



Indecainide

Cardiac Electrophysiological Effects. The drugs in class I_C bind tightly to and block fast Na^+ channels. Thus, they decrease the $\dot{V}_{max}$ and overshoot of action potentials in atrial, ventricular, and Purkinje fibers and slow conduction in these structures, most prominently in the His–Purkinje system (*see* Symposium, 1984c, 1984d, 1986). There are relatively small effects on repolarization, duration of action potentials, and the ERP in Purkinje fibers. The refractory period of the AV node is usually increased and refractory periods in accessory pathways are markedly prolonged by these drugs. In addition, propafenone has weak β-adrenergic blocking effects.

Electrocardiographic Effects. At therapeutic concentrations in man, class-I_C drugs have little effect on heart rate; however, they cause a substantial increase in the P–R interval and the duration of the QRS complex (Symposium, 1984c, 1984d, 1986). The P–R interval may increase to 0.30 second and the QRS complex may be prolonged to 0.18 second; the dose should be reduced if these values are exceeded. The Q–T_c interval may be prolonged due to marked widening of the QRS complex, but the J–T interval (from end of QRS to the end of the T wave) always shortens. Clinical electrophysiological studies reveal a substantial increase in the P–A, A–H, and H–V intervals; the latter may lengthen by 15 to 20 msec, more than that observed with any other class of antiarrhythmic drugs.

Absorption, Distribution, and Elimination. *Flecainide.* Flecainide is almost completely absorbed after oral administration; peak concentrations in plasma occur at about 3 hours. Flecainide is metabolized by the liver; about 40% is excreted in the urine unchanged. The metabolites have little or no antiarrhythmic activity. The average half-time of elimination is about 11 hours. Flecainide may accumulate in patients with renal failure, and its concentration in plasma and the ECG should be carefully monitored during treatment of such patients (Symposium, 1984c; Roden and Woosley, 1986a).

Encainide. Encainide is also almost completely absorbed after oral administration, but its bioavailability is reduced to about 30% by first-pass hepatic metabolism. Peak concentrations in plasma occur at 30 to 90 minutes. Encainide is metabolized by the hepatic cytochrome P_{450} system and has a half-life in plasma of 2 to 3 hours. About 10% of the population have a genetically determined deficiency in this

P_{450} system; the bioavailability increases to greater than 80% and the half-life is prolonged to 10 to 12 hours in such individuals. Two active metabolites are formed: O-desmethylencainide (half-life of 3 to 4 hours) and 3-methoxy-O-desmethylencainide (half-life of 6 to 12 hours). While the parent compound is responsible for the effects of the drug in the 10% of patients who metabolize encainide slowly, these metabolites account for most of the antiarrhythmic actions of encainide in the majority of patients. They accumulate in the plasma of patients with renal failure, thus necessitating a reduction in dosage (Symposium, 1986; Woosley *et al.*, 1988).

Propafenone. Although propafenone is almost completely absorbed from the gastrointestinal tract, its bioavailability is reduced by extensive first-pass hepatic metabolism and is dose dependent; values range from 5 to 40% for patients with normal hepatic function or up to 60% in those with severe liver disease (*see* Symposium, 1984d). Peak concentrations in plasma occur at about 3 hours. Propafenone is 97% bound to α_1-acid glycoprotein. The drug is almost completely metabolized in the liver before excretion, primarily in the feces. At least 11 metabolites have been detected; two compounds, 5-hydroxypropafenone and N-desalkylpropafenone, have electrophysiological effects similar to those of the parent drug. The steady-state concentrations of each of these metabolites in plasma is about 20% of that of propafenone. Like encainide, rates of hepatic metabolism of propafenone are bimodally distributed in the population. The elimination half-life of propafenone averages 5 to 6 hours in fast metabolizers and 17 hours in slow metabolizers; dosage should be reduced for the latter individuals. These values may increase up to twofold in patients with severe hepatic dysfunction. The pharmacokinetic properties of propafenone are dose dependent; for example, an increase in dose from 300 to 900 mg per day can result in as much as a tenfold increase in its concentration in plasma.

Indecainide. Indecainide is almost completely absorbed after oral administration; peak concentrations in plasma occur at about 1 to 2 hours. About 50% of the drug is bound to plasma proteins. Indecainide is eliminated with a half-time of around 8 hours, principally by renal excretion of the unchanged drug; the dosage should be reduced in patients with compromised renal function. The principal metabolite of indecainide, N-desalkylindecainide, has substantial antiarrhythmic activity; its concentration in plasma is usually about 20% of that of indecainide.

Preparations, Dosage, and Routes of Administration. *Flecainide. Flecainide acetate* (TAMBOCOR) is available for oral administration as 50-, 100-, and 150-mg tablets. The initial dose is 100 mg twice a day. Dosage may be increased every 4 days in increments of 100 mg per day to a maximum of 400 to 600 mg per day given in two or three portions. Therapeutic effects are usually achieved at concentrations of 0.2 to 1.0 μg of flecainide per milliliter of plasma; the probability of toxicity increases when the concentration exceeds 1.0 μg/ml.

Encainide. Encainide hydrochloride (ENKAID) is supplied for oral administration as 25-, 35-, and 50-mg capsules. The initial dose is 25 mg given three times a day; this can be increased every 3 to 5 days to a maximum of 50 mg four times a day. It may be necessary to adjust dosage in patients with renal or hepatic impairment.

Therapeutic Uses. Flecainide and encainide are indicated for life-threatening ventricular arrhythmias; propafenone and indecainide may eventually be found to be similarly useful. The use of these drugs should be initiated in hospital for patients with malignant ventricular arrhythmias, symptomatic congestive heart failure, bifascicular block, or sinus node dysfunction. These drugs are under investigation for the treatment of supraventricular tachycardia and paroxysmal atrial fibrillation (Symposium, 1988a, 1988b).

Untoward Effects. All drugs in class I_C produce similar adverse cardiac effects. Proarrhythmic effects occur in 8 to 15% of patients with malignant ventricular arrhythmias, but such effects were thought to be rare in patients with benign or potentially malignant ventricular arrhythmias (Morganroth *et al.*, 1986). However, encainide and flecainide have recently been shown to increase the risk of sudden death and cardiac arrest in patients who have had a myocardial infarction and who have asymptomatic unsustained ventricular arrhythmias (CAST Investigators, 1989). For this reason, these drugs are no longer indicated for benign or potentially malignant ventricular arrhythmias. All of these drugs can aggravate sinus node dysfunction; heart failure can also be aggravated, but this effect seems most prominent for flecainide and indecainide. High therapeutic doses of flecainide and encainide cause visual disturbances; 10 to 15% of patients treated with flecainide have such symptoms, usually blurred or double vision on quick, far lateral gaze. Propafenone has been associated with granulocytopenia and with a SLE-like syndrome. The concentrations of flecainide, encainide, and propafenone in plasma increase during concurrent administration of cimetidine.

CLASS II: β-ADRENERGIC ANTAGONISTS

The pharmacology of the β-adrenergic blocking agents is discussed in Chapter 11. Only properties related to their use in the treatment of cardiac arrhythmias are considered here. Propranolol, acebutolol, and esmolol are indicated for the treatment of arrhythmias. Metoprolol, propranolol, and timolol are used prophylactically after myocardial infarction to reduce the incidence of sudden death in these patients.

Cardiac Electrophysiological Effects. Most of the antiarrhythmic effects of β-adrenergic antagonists can be explained by their selective blockade of β receptors. Propranolol is known to have two other direct actions that may be relevant to its antiarrhythmic activity: it increases background outward current (i_{K_1}) and, in high concentrations, it significantly depresses i_{Na} (membrane-stabilizing action).

Automaticity. β-Adrenergic stimulation causes a marked increase in the slope of phase-4 depolarization and in the spontaneous firing rate of the sinus node. This effect is competitively blocked by β-adrenergic antagonists. The effect on sinus rate is small when catecholamines are absent. However, blockade of β receptors can cause severe slowing of sinus rate in patients with preexisting sinus node disease (Strauss *et al.*, 1976). There are also significant inhibitory effects on automaticity in cardiac Purkinje fibers when their firing rate has been increased by catecholamines. Under some circumstances, cardiac Purkinje fibers require the action of catecholamines to sustain their spontaneous activity. In this case, β-adrenergic antagonists can totally abolish automaticity in the His–Purkinje system. At low concentrations, propranolol increases outward background current, i_{K_1}, in Purkinje fibers, as do lidocaine and phenytoin; this action decreases automaticity as well (Stagg and Wallace, 1974). Other β-adrenergic antagonists in clinical use appear to lack this action.

Excitability and Threshold. The electrical threshold of the atria and ventricles of normal dogs is not affected by β-adrenergic blockade, but the threshold for fibrillation after experimental infarction is increased (Gang *et al.*, 1984).

Responsiveness and Conduction. Only very high concentrations of propranolol (*e.g.*, 1000 to 3000 ng/ml) decrease responsiveness in Purkinje fibers (Davis and Temte, 1968). These concentrations are much higher than those needed for substantial β-adrenergic blockade (100 to 300 ng/ml). However, concentrations over 1000 ng/ml are sometimes required for control of ventricular arrhythmias (Woosley *et al.*, 1977). Low-amplitude premature responses are abolished by propranolol (Davis and Temte, 1968). These effects are similar to those seen with lidocaine or phenytoin and are probably due to an increase in g_{K_1}. Different effects may occur in abnormal fibers. In the dog heart *in situ*, propranolol causes slowing of intramyocardial conduction in muscle that is made acutely ischemic. It has no such effect on normal portions of the ventricle (Kupersmith *et al.*, 1976). Slow responses can be dependent on catecholamines, as can afterdepolarizations; β-adrenergic blockers ameliorate arrhythmias caused by these mechanisms.

Duration of the Action Potential and Refractoriness. Blockade of β receptors has little effect on the duration of action potentials in the sinus node, atrium, or AV node; the effect on action potentials in ventricular muscle or Purkinje fibers is variable. All β-adrenergic blocking drugs cause a substantial increase in the ERP of the AV node; this action is the basis for the major uses of these drugs as antiarrhythmic agents.

Effect on Reentrant Arrhythmias. In supraventricular tachycardia due to AV nodal reentry, the β-adrenergic antagonists abolish reentry by increasing AV nodal refractoriness. In the ventricles, these drugs abolish slow responses that are dependent on catecholamines. In addition, propranolol can repolarize tissues that have been depolarized by stretch or low $[K]_o$, and thus enhances fast responses in ischemic ventricular muscle. In higher concentration, propranolol and acebutolol have "quinidine-like" effects on phase-0 depolarization and responsiveness of Purkinje fibers. In addition, β-adrenergic antagonists may favorably influence arrhythmias by decreasing myocardial oxygen utiliza-

tion, thereby reducing myocardial ischemia.

Electrocardiographic Effects. β-Adrenergic blockade causes a small increase in the P–R interval but has no effect on the duration of the QRS complex. Effects on the $Q–T_c$ interval vary with individual drugs. In man, β-adrenergic blockade causes a substantial increase in the ERP of the AV node, but there is no increase in the H–V interval (Seides *et al.*, 1974).

Autonomic Nervous System Effects. All β-adrenergic blocking drugs that are used to treat arrhythmias leave vagal and α-adrenergic mechanisms intact. Propranolol blocks both β_1- and β_2-adrenergic receptors and has substantial local anesthetic (membrane-stabilizing) actions, but it exhibits no intrinsic sympathomimetic activity. Both acebutolol and esmolol are relatively selective β_1-adrenergic antagonists; the former drug possesses significant intrinsic sympathomimetic activity and membrane-stabilizing actions, while the latter does not. A detailed discussion of β-adrenergic antagonists is presented in Chapter 11.

Absorption, Distribution, and Elimination. *Propranolol.* Intestinal absorption of propranolol is excellent, but extensive first-pass metabolism reduces bioavailability to about 25% (*see* Chapter 11; Appendix II). Its half-time for elimination is about 4 hours. As with lidocaine, the hepatic extraction of propranolol is very high and elimination is significantly reduced when hepatic blood flow decreases. Propranolol may decrease its own elimination rate by decreasing cardiac output and hepatic blood flow, particularly in patients with left ventricular dysfunction.

Acebutolol. Like propranolol, acebutolol is well absorbed from the gastrointestinal tract, and its oral bioavailability is less than 50%; substantially higher values occur in elderly patients, and reduction of dosage may be required. The principal metabolite is N-acetylacebutolol (diacetolol), which is equipotent as a β blocker and even more selective for β_1 receptors as compared with the parent drug. The elimination half-time of acebutolol is about 3 hours and that of diacetolol is 8 to 12 hours. Diacetolol is eliminated largely by urinary excretion; lower doses of acebutolol are thus required for patients with renal failure.

Esmolol. Esmolol is given only by intravenous infusion; it distributes to tissues with a half-time of 2 minutes. The ester bond of esmolol is hydrolyzed rapidly by esterases in red blood cells. The elimination half-time is about 8 minutes and the metabolites are inactive.

Dosage and Routes of Administration. *Propranolol.* Propranolol is primarily given orally for long-term treatment of cardiac arrhythmias. Concentrations in plasma that are associated with therapeutic effects vary widely (20 to 1000 ng/ml) and depend on the arrhythmia being treated. The dosage ranges from 30 to 320 mg per day for treatment of arrhythmias that are sensitive to effects of the drug. As much as 1000 mg a day may be needed to suppress some ventricular arrhythmias. Propranolol is effective when given three to four times a day. The duration of action can be prolonged by the administration of large doses, since β-adrenergic blocking agents have a greater margin of safety than do most antiarrhythmic drugs. For emergency use, propranolol can be injected intravenously; 1 to 3 mg is given over several minutes with careful monitoring of the ECG, arterial blood pressure, and pulmonary arterial pressure (by means of a Swan–Ganz catheter); this dose may be repeated after a few minutes if necessary. Much lower doses are needed to achieve a given plasma concentration when given intravenously than after oral administration because first-pass hepatic extraction is avoided.

Acebutolol. Acebutolol is given orally for the treatment of cardiac arrhythmias. The usual initial dose is 200 mg taken twice a day. The dosage is gradually increased to a maximum daily dose of 600 to 1200 mg given in two portions.

Esmolol. Esmolol is administered intravenously for short-term or emergency treatment of supraventricular tachycardias. Dosage regimens are discussed in Chapter 11. After control of ventricular rate is achieved, long-term oral therapy is instituted with an appropriate drug.

Therapeutic Uses. *Supraventricular Arrhythmias.* Propranolol is used primarily to treat supraventricular tachyarrhythmias such as atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachycardia. For these arrhythmias, the objective of therapy usually is to slow the ventricular rate rather than to abolish the arrhythmia. Propranolol accomplishes this objective by blocking β-adrenergic influences on the AV

node, thereby increasing refractoriness of the AV node. Only rarely does propranolol convert these supraventricular arrhythmias to sinus rhythm. Not infrequently, propranolol and digitalis will successfully control the ventricular rate in patients with atrial fibrillation or flutter when maximal doses of digitalis alone do not; this additive effect may result from the fact that digitalis increases vagal tone, while propranolol blocks β-adrenergic influences on the AV node.

Combination therapy with quinidine and propranolol probably improves the likelihood of converting atrial fibrillation to sinus rhythm. Propranolol has been helpful in preventing paroxysmal supraventricular tachycardia due to AV nodal reciprocation and the paroxysmal supraventricular tachycardia of the Wolff–Parkinson–White syndrome alone or in combination with quinidine. In the latter condition, quinidine increases the refractoriness of the accessory AV connection and propranolol can be relied upon to increase AV nodal refractoriness. Esmolol is indicated for rapid control of ventricular rate in patients with atrial flutter or fibrillation in postoperative or other emergency circumstances in which control with a short-acting agent is desirable (Angaran *et al.*, 1986).

Ventricular Arrhythmias. Doses of propranolol of as much as 320 mg per day are not likely to be effective against ventricular arrhythmias except in special circumstances. Propranolol is an excellent choice for treatment of symptomatic ventricular premature depolarizations in patients without structural heart disease; the drug often markedly reduces symptoms, even when the arrhythmia is not greatly affected. When ventricular arrhythmias are triggered by exercise or emotion, smaller doses of propranolol (*e.g.*, 80 to 160 mg per day) are very likely to prevent them. In patients with ischemic heart disease, propranolol may ameliorate ventricular arrhythmias by preventing or reducing ischemia. However, most ventricular arrhythmias respond incompletely or not at all to conventional doses of propranolol. Large doses of propranolol (500 to 1000 mg a day) may be required to control ventricular arrhythmias (Woosley *et al.*, 1979). Acebutolol is indicated for the management of ventricular premature complexes (Singh *et al.*, 1986). Propranolol is the drug of choice for severe ventricular arrhythmias in the prolonged Q–T syndrome; when propranolol fails, removal of the left stellate ganglion may be effective (Schwartz, 1984; Moss *et al.*, 1985; Moss, 1986).

Three large, randomized, placebo-controlled trials with timolol (10 mg twice a day), propranolol (60 or 80 mg three times a day), and metoprolol (100 mg twice a day) showed that treatment with these β-adrenergic antagonists was effective for reducing death and nonfatal myocardial infarction in the year after acute myocardial infarction (Beta-Blocker Heart Attack Study Group, 1981; Norwegian Multicenter Study Group, 1981; Symposium, 1984a).

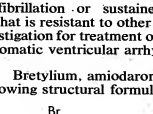
Digitalis-Induced Arrhythmias. Propranolol abolishes ventricular arrhythmias induced by digitalis by effects both directly on the heart and, probably, on the CNS. However, the incidence of adverse effects (*e.g.*, sinus bradycardia or AV block) during treatment of digitalis-induced arrhythmias with propranolol is higher than with phenytoin or lidocaine.

Untoward Effects. In patients with ventricular failure, the level of sympathetic activity is high and can provide significant support to the ventricle. Therefore, when β-adrenergic antagonists are used as antiarrhythmic drugs, significant hypotension or left ventricular failure can occur. However, many patients who have ventricular failure can tolerate long-term oral therapy with propranolol if digitalis, vasodilators, or diuretics are used concomitantly. The potent effect of β-adrenergic blockade on conduction in the AV node can also lead to serious adverse effects, such as AV block or asystole. Sudden withdrawal of β-adrenergic antagonists in patients with angina pectoris can precipitate worsening of angina, cardiac arrhythmias, and acute myocardial infarction. Other untoward effects are described in Chapter 11.

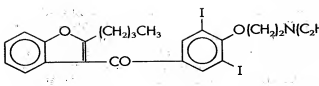
Class III: Bretylium, Amiodarone, and Sotalol

The drugs in class III possess diverse pharmacological properties. However, they all share the capacity to prolong the duration of action potentials and refractoriness in Purkinje and ventricular muscle fibers. All of these drugs have significant interactions with the autonomic nervous system. Bretylium was approved in 1978 for emergency treatment of drug-resistant ventricular fibrillation or sustained ventricular tachycardia. Amiodarone was approved in 1986 for the treatment of recurrent ventricular fibrillation or sustained ventricular tachycardia that is resistant to other drugs. Sotalol is under investigation for treatment of life-threatening or symptomatic ventricular arrhythmias.

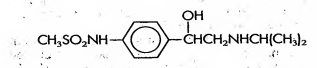
Chemistry. Bretylium, amiodarone, and sotalol have the following structural formulas.



Bretylium



Amiodarone



Sotalol

Cardiac Electrophysiological Effects. *Duration of the Action Potential and Refractoriness.* All class-III drugs prolong the action potential duration and the ERP of Purkinje fibers and ventricular muscle cells. Except for bretylium, these drugs produce similar but less intense effects on these parameters in atrial and AV nodal cells.

Automaticity. There is little direct effect of the drugs in class III or automaticity in the sinus node and the His–Purkinje system. Bretylium briefly increases automaticity immediately after its injection by releasing norepinephrine from sympathetic nerve terminals. These effects can be prevented experimentally by prior depletion of catecholamines with reserpine or clinically by β-adrenergic blockade (Bigger and Jaffe, 1971). Amiodarone substantially decreases the automaticity of the sinus node and the His–Purkinje system by mechanisms that are not understood; the drug (or its metabolites) may possess noncompetitive β-adrenergic blocking actions. Sotalol decreases automaticity, presumably because it is a β-adrenergic antagonist (Carmeliet, 1985).

Excitability and Threshold. The class-III drugs have little effect on diastolic electrical current threshold. However, they substantially increase the threshold for ventricular fibrillation (Kniffen *et al.*, 1975; Symposium, 1983; Lynch *et al.*, 1984).

Responsiveness and Conduction. Bretylium and sotalol have no significant effect on membrane responsiveness or conduction in cardiac Purkinje fibers. Amiodarone binds to inactivated Na^+ channels and decreases membrane responsiveness and conduction in Purkinje fibers (Mason *et al.*, 1984). Conduction through the AV node is decreased significantly by sotalol and amiodarone, but is little affected by bretylium.

Effect on Reentrant Arrhythmias. Amiodarone, bretylium, and sotalol are thought to terminate reentrant arrhythmias by markedly prolonging refractoriness without affecting propagation of the cardiac impulse (Singh and Nademanee, 1985). In addition, bretylium may cause repolarization and increased rate of conduction in abnormal depolarized regions by releasing catecholamines.

Electrocardiographic Effects. At therapeutic concentrations in man, amiodarone and sotalol decrease heart rate; bretylium causes little change. During long-term treatment with amiodarone, symptomatic sinus bradycardia can develop. Amiodarone and sotalol, but not bretylium, cause a substantial increase in the P–R interval. All three drugs prolong the Q–T_c, J–T, P–A, and A–H intervals. Only amiodarone increases the H–V interval and the duration of the QRS complex (Mason, 1987).

Autonomic Nervous System Effects. None of these three drugs alters vagal reflexes or the responsiveness of cardiac cholinergic receptors. Sotalol is a β-adrenergic antagonist, while amiodarone causes some noncompetitive α- and β-adrenergic blockade. Like guanethidine, bretylium is taken up and concentrated in adrenergic nerve terminals (*see* Chapter 33). Initially, bretylium releases norepinephrine from nerve terminals; later, it prevents release of the transmitter. It does not depress conduction in sympathetic nerves, impair transmission across ganglia, deplete the adrenergic neuron of norepinephrine, or decrease the responsiveness of adrenergic receptors. During long-term treatment with bretylium, adrenergic receptors show increased responsiveness to circulating catecholamines.

Hemodynamic Effects. None of the three drugs in class III directly decreases the contractility of the mammalian myocardium. However, β-adrenergic blockade with sotalol can reduce cardiac function in patients who are dependent upon the sympathetic nervous system to maintain a normal cardiac output. Although bretylium can increase myocardial contractility transiently by releasing catecholamines, it can also cause orthostatic hypotension by blockade of sympathetic cardiovascular reflexes (Chatterjee *et al.*, 1973). Amiodarone can decrease myocardial oxygen demand and enhance cardiac performance because it relaxes vascular smooth muscle and decreases systemic and coronary vascular resistance.

Absorption, Distribution, and Elimination. *Bretylium.* Oral absorption of bretylium is poor, as would be expected of a quaternary amine. After intramuscular administration, bretylium is eliminated almost entirely by renal excretion, without significant metabolism. The average half-time for elimination is about 9 hours; half-times of 15 to 30 hours occur in patients with renal insufficiency (*see* Heissenbuttel and Bigger, 1979).

Amiodarone. Oral doses of amiodarone are poorly and slowly absorbed; the bioavailability is about 45%, with marked interindividual variability. Peak concentrations in plasma occur about 5 to 6 hours after an oral dose. Amiodarone is extensively bound to tissues and is metabolized slowly in the liver. The elimination of the drug displays complex pharmacokinetic properties, but the half-time of its elimination is estimated to be about 25 to 60 days. During long-term treatment with amiodarone, the active desethyl derivative accumulates in plasma, and its concentration may exceed that of the parent compound.

Sotalol. Oral doses of sotalol are readily absorbed, and the bioavailability is nearly 100%. Maximum concentrations in plasma are reached 2

to 3 hours after administration, and only a small fraction of the drug is bound to plasma proteins. The half-life of elimination from plasma is about 10 to 15 hours. The elimination of sotalol is almost entirely by urinary excretion of unchanged drug, and dosage must be reduced in patients with renal failure.

Preparations, Dosage, and Routes of Administration. *Bretylium.* Bretylium is available as *bretylium tosylate* (BRETYLOL) in a solution containing 50 mg/ml. The drug is diluted to a concentration of 10 mg/ml or less, and a dose of 5 to 10 mg/kg is infused over 10 to 30 minutes; subsequent doses can be given at intervals of 1 to 2 hours if the arrhythmia persists or every 6 hours for maintenance. The dosing interval should be increased in patients with impaired renal function. In emergencies, such as during cardiac resuscitation, a dose of 5 mg/kg of the undiluted solution can be injected intravenously; if ventricular fibrillation persists, the dose may be increased to 10 mg/kg and repeated as necessary. For intramuscular administration, undiluted bretylium tosylate should be used, and the dose of 5 to 10 mg/kg is repeated every 1 to 2 hours if the arrhythmia persists or every 6 to 8 hours for maintenance.

Amiodarone. Amiodarone hydrochloride (CORDARONE) is supplied as 200-mg tablets. Because it can take several months to reach full effect, loading doses of 800 to 1600 mg per day are given for 1 to 3 weeks in hospital, with continuous electrocardiographic monitoring. Then, daily doses of 600 to 800 mg are given (usually for 4 weeks) before maintenance treatment is started with 400 to 600 mg per day. Treatment is evaluated after 2 to 8 weeks, usually with programmed ventricular stimulation. The drug is continued if the sustained ventricular arrhythmia becomes noninducible or is slowed enough to be asymptomatic. Long-term effective treatment has been associated with plasma concentrations of 1.0 to 2.5 μg/ml.

Sotalol. Sotalol is not yet available for general use in the United States, and its formulation has not been finalized. Doses of 80 to 320 mg twice a day have been used to treat ventricular arrhythmias. The initial dose is usually 80 mg twice a day and is increased as needed every 3 or 4 days. Efficacy is evaluated either by 24-hour ECG recordings or by programmed ventricular stimulation.

Therapeutic Uses. Bretylium is currently recommended only for treatment of life-threatening ventricular arrhythmias that fail to respond to adequate doses of a first-line antiarrhythmic drug such as lidocaine or procainamide. Use of bretylium should be limited to intensive care facilities. The response of severe, refractory ventricular fibrillation has been impressive (*see* Heissenbuttel and Bigger, 1979; Symposium, 1984b). Ventricular tachycardia usually responds only after some time—6 hours or more after administration of a dose.

Because of its long half-life and life-threatening adverse effects (*see* below), amiodarone is indicated only for recurrent ventricular fibrillation and recurrent, hemodynamically unstable sustained ventricular tachycardia. Treatment should always be started in hospital, and efficacy must be assessed with a provocative approach (usually programmed ventricular stimulation). Thus, amiodarone should be used only in hospitals with electrocardiographic monitoring and clinical electrophysiological facilities. Intravenous use of amiodarone is under investigation for the emergency treatment of persistent or frequently recurring, life-threatening ventricular arrhythmias.

Sotalol is apparently a much safer drug than amiodarone, and it may become a good first choice for the treatment of malignant ventricular arrhythmias, as well as for benign or potentially malignant ventricular arrhythmias. Sotalol appears to be effective for the treatment of paroxysmal supraventricular tachycardia and atrial fibrillation, but comparative studies have not yet firmly positioned it relative to alternative modes of treatment.

Untoward Effects. Hypotension is the principal undesirable effect of bretylium when it is used intravenously to treat acute arrhythmias. Orthostatic hypotension is usually significant, and supine hypotension is common. Rapid intravenous administration may cause nausea and vomiting. Tricyclic antidepressant drugs can prevent uptake of bretylium by adrenergic nerve terminals.

Adverse effects of amiodarone are common and increase markedly after a year of treatment; they affect many organ systems, and some cause death (Mason, 1987). More than 75% of patients treated for 1 to 2 years experience adverse effects and 25 to 33% discontinue treatment because of them. Symptomatic pulmonary toxicity occurs in 10 to 15% of those treated for 1 to 3 years and can cause death in about 10% of those so affected. Hepatic injury is common but is rarely fatal. Aggravation of arrhythmias occurs in 2 to 5% of patients receiving the drug. Asymptomatic corneal microdeposits occur in all. Cutaneous photosensitivity occurs in 10 to 15% and blue discoloration in about 5% during long-term therapy. Amiodarone inhibits the peripheral conversion of thyroxine to triiodothyronine; although symptomatic hypothyroidism occurs in 5% and hyperthyroidism in 2% of patients, abnormal tests of thyroid function are much more common. Substantial increases in LDL-cholesterol concentrations are frequently observed.

Sotalol has the typical adverse effects of a β-adrenergic blocking agent (*see* Chapter 11). In a large controlled trial, treatment with the drug was discontinued because of the development of heart failure (1%), proarrhythmias (2.5%), and bradycardia (3%). *Torsades de pointes* occurs in about 2% of the patients treated with sotalol for malignant ventricular arrhythmias, usually in the first week of treatment and after the $Q\text{–}T_c$ interval is substantially prolonged. The $Q\text{–}T_c$ interval should be monitored during treatment and consideration given to decreasing the dosage of sotalol if it exceeds 0.50 second.

Drug Interactions. Amiodarone increases the plasma concentrations and effects of digoxin, warfarin, quinidine, procainamide, phenytoin,

encainide, flecainide, and diltiazem. Amiodarone increases the likelihood of bradycardia, sinus arrest, and AV block when β-adrenergic antagonists or Ca^{2+}-channel blockers are administered concurrently. Because of its slow elimination, the potential for interactions and other adverse effects persists for many weeks after amiodarone is discontinued.

Class IV: Verapamil and Diltiazem

The antiarrhythmic agents in Class IV are Ca^{2+}-channel blockers. The clinically important consequences of this action for the treatment of arrhythmias are depression of Ca^{2+}-dependent action potentials and slowing of conduction in the AV node. Verapamil is the only Ca^{2+}-channel blocker that is currently marketed as an antiarrhythmic drug; the efficacy and safety of diltiazem for the treatment of supraventricular arrhythmias are being evaluated.

Verapamil, a derivative of papaverine, blocks Ca^{2+} channels (principally L channels) in the membranes of smooth and cardiac muscle cells. In 1981, verapamil was approved in the United States for treatment of angina pectoris and supraventricular arrhythmias. The general discussion of Ca^{2+}-channel blockers appears in Chapter 32, Discussion here is confined to their use in treating arrhythmias.

Cardiac Electrophysiological Effects. Verapamil and diltiazem have direct effects on the electrical and mechanical properties of heart muscle and vascular smooth muscle cells.

Impulse Formation. Verapamil and diltiazem slow the spontaneous firing of pacemaker cells in the sinus node *in vitro*. However, in intact animals and in man the heart rate slows only minimally because this direct effect is counteracted by increased reflex sympathetic activity resulting from arterial vasodilatation.

Verapamil decreases the rate of phase-4 spontaneous depolarization in cardiac Purkinje fibers (Danilo *et al.*, 1980) and can block the delayed afterdepolarizations and triggered activity seen in experimental digitalis toxicity (Rosen and Danilo, 1980).

Effect on Reentrant Arrhythmias. The most marked effect of verapamil or diltiazem is to decrease the conduction velocity through the AV node and increase its functional refractory period. The effect on AV nodal conduction is presumably a direct result of Ca^{2+}-channel blockade, but it is not prominent at concentrations of certain other Ca^{2+}-channel blockers (*e.g.*, nifedipine) that are achieved clinically. Depression of the AV node is responsible for slowing the ventricular response to atrial flutter or fibrillation and termination of paroxysmal supraventricular tachycardia.

Electrocardiographic Effects. Verapamil and diltiazem increase the P–R interval in sinus rhythm and slow the ventricular rate substantially in patients with atrial fibrillation.

Autonomic Nervous System Effects. Neither verapamil nor diltiazem has cholinergic or β-adrenergic blocking properties. However, verapamil does have appreciable α-adrenergic blocking activity.

Absorption, Distribution, and Elimination. The pharmacokinetic properties of verapamil and diltiazem are discussed in Chapter 32 (*see also* Appendix II).

Dosage and Routes of Administration. To convert PSVT to sinus rhythm, a dose of 5 to 10 mg of verapamil is given intravenously over at least 2 to 3 minutes. To obtain rapid control of the ventricular rate in atrial fibrillation or atrial flutter, 10 mg of verapamil can be given intravenously over 2 to 5 minutes, and this dose can be repeated in 30 minutes if necessary. To prevent recurrences of PSVT or to control the ventricular response to atrial fibrillation, oral doses of 240 to 480 mg per day are given in three to four divided portions.

Although not yet an approved indication, oral doses of 60 to 90 mg of diltiazem given every 6 hours have been used for prophylaxis against PSVT.

Therapeutic Uses. *Supraventricular Arrhythmias.* Verapamil has become the drug of first choice for abolishing acute episodes of paroxysmal supraventricular tachycardia due to AV nodal reentry or due to anomalous AV connections. Verapamil is also very useful for immediate reduction of the ventricular response to atrial fibrillation or atrial flutter unless the arrhythmia is associated with the Wolff–Parkinson–White syndrome. In man, intravenous verapamil (75 μg/kg) slows the ventricular response to atrial fibrillation by about 30%. Atrial tachycardia with AV block caused by digitalis

toxicity may be a manifestation of delayed afterdepolarizations and triggered activity. Verapamil could be effective in abolishing this arrhythmia, but its use is too risky because it can cause additional AV block and suppress automaticity in the His–Purkinje system. Diltiazem has similar effects but is not yet approved for this use.

Ventricular Arrhythmias. Verapamil and diltiazem do not have a major role in the treatment of ventricular arrhythmias. Verapamil and diltiazem are used to treat ventricular tachycardia and ventricular fibrillation caused by coronary artery spasm; they prevent spasm and improve the tolerance of ventricular tissues to ischemia, rather than having a significant direct antiarrhythmic effect.

Untoward Effects. The principal adverse effects of verapamil and diltiazem are cardiac and gastrointestinal. Intravenous use of these drugs is contraindicated in patients who have hypotension, severe heart failure, sick sinus syndrome, AV block, atrial fibrillation, Wolff–Parkinson–White syndrome, or ventricular tachycardia (McGovern *et al.*, 1986). Verapamil can increase the ventricular rate when given intravenously to patients with the Wolff–Parkinson–White syndrome and atrial fibrillation. This is due to reflex increases in sympathetic nervous activity (Gulamhusein *et al.*, 1982); in some patients, a reduction of the ERP in the bundle of Kent also contributes to the increase in the ventricular rate. Verapamil can also cause severe hypotension or ventricular fibrillation in patients with ventricular tachycardia (Rankin *et al.*, 1987). Unexpected sinus bradycardia, AV block, left ventricular failure, or hypotension can occur in elderly patients after intravenous administration of verapamil. Lower doses and a slower rate of injection should thus be used in patients over the age of 60. The major gastrointestinal adverse effect of verapamil is constipation, but gastric upset and other upper gastrointestinal symptoms can occur as well. Diltiazem is better tolerated in this regard.

Drug Interactions. Concurrent use of verapamil and β-adrenergic blocking agents or digitalis can lead to significant bradycardia or AV block. The main reason for this is the additive effects of these drugs on the sinus or AV nodes. In addition, verapamil interacts with digoxin in a manner similar to the quinidine–digoxin interaction (*see* Chapter 34). Concomitant use of verapamil or diltiazem with antihypertensive drugs that depress the sinus node (*e.g.*, reserpine or methyldopa) can intensify sinus bradycardia.

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